A.M.A. ARCHIVES OF
NEUROLOGY & PSYCHIATRY

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ORIGINAL ARTICLES

A. M. A.
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Late Cerebral Changes Incident to Severe Hypoglycemia (Insulin Shock)

Their Relation to Cerebral Anoxia

CYRIL B. COURVILLE, M.D., Los Angeles

The fact that acute severe degrees of hypoglycemia may result in symptoms referable to the brain and that in event of fatal issue such symptoms are accompanied by structural changes in the central nervous tissues has been recognized for some years. The resulting cerebral (rarely cerebellar) lesions were at first considered to be a consequence of the toxic effect of insulin. This conclusion did not seem illogical at the time, for in cases with short survival period the alterations in the gray matter were not particularly specific. As time has gone on, however, the recognition of the total pathological picture of severe insulin shock proves the lesion complexes to be remarkably similar to, if not identical with, those of cerebral anoxia of various etiologies.

The kaleidoscopic picture of cerebral anoxia has come to be fairly well defined.[1-6] With some relatively minor differences in the end-picture due to variations in the

mechanism by which the damage was produced, the occurrence of widespread, though not uniform, changes in the cerebral cortex and basal ganglia is to be expected. In cases with short survival periods these changes are characteristically congestive, together with diffuse neuronal changes, sometimes associated with an irregular, patchy loss of nerve cells. As the survival interval is increasingly lengthened, focal, then laminar, necrosis becomes more evident, with a more or less profound disturbance in the cortical and ganglionic architecture.

My discovery of widespread and profound changes in the cerebral gray matter in two cases of severe hypoglycemia which were similar to those observed in instances of severe cerebral anoxia after nitrous oxide anesthesia, carbon monoxide asphyxia, and mechanical strangulation raised the question of their possible relationship.[7] The brain in seven such cases, with death the result of severe hypoglycemic shock, has been studied in the Cajal Laboratory. In two cases death occurred within a short interval of time, the only significant finding in the brain being that of acute congestion. In two other cases with delayed exitus (one reported elsewhere),[8] the hypoglycemic state was due to an islet adenoma of the pancreas.

In another case, with a history of many episodes of hypoglycemia, the findings were those of widespread focal and laminar loss of nerve cells. In the remaining two instances to be described herewith, death was the ultimate result of an overdosage of insulin in the treatment of diabetes, although the patients survived for intervals of 137 and 86 days, respectively.

It is because such cases of prolonged survival are rare, and because it is this type of case which sheds most light on the probable mechanism of cerebral damage, that it is proposed to place on record the significant features of these two examples of "insulin shock." At the same time an analysis of the probable pathogenesis of cerebral damage will also be made. A brief survey of the pertinent literature will precede report of these two cases.

Review of Literature on the Cerebral Pathology of Insulin Shock

The knowledge that overdosage of insulin is capable of producing severe and irreversible changes in the brain dates back almost to the discovery of insulin itself. Ehrmann and Jacoby[9] noted the occurrence of focal subarachnoid and small intracerebral hemorrhages in 9 out of 12 fatal cases of acute hypoglycemic shock. Wohlwill[10] observed a generalized change in the cerebral nerve cells in the second of two cases after survival of approximately five days. Terplan[11] pointed out that alterations in the nerve cells were most conspicuous and widespread in Lamina III of the cortex. He also noted an early swelling of the endothelial cells of the capillary blood vessels. Focal loss of cortical nerve cells and disappearance of the small nerve cells of the corpus striatum were reported by Cammermeyer.[12] In Bodechtel's case,[13] the cortical changes were similar but even severer. It was also noted that glial changes (proliferation) were dependent upon severe damage to the cortex and basal ganglia.[14] Such

changes, accompanied by early softening, led to actual proliferation of the endothelial cells and the formation of new capillaries.[15] Involvement of multiple laminae (III and IV) with "dropping-out" of nerve cells was also described by Kobler.[16]

The case reported by Döring[17] deserves special mention in that large, circumscribed foci of red softening were noted in the cerebral cortex, particularly in the parieto-occipital region. The essential contribution of Ferraro and Jervis,[18] based on a study of four cases with autopsy verification, was to point out the variety of cellular and architectural changes (focal devastation or necrosis, diffuse laminar necrosis, patchy loss of nerve cells, and variation in the nature and degree of injury to individual nerve cells). In the case reported by Sahs and Alexander,[19] the variety of vascular changes, both functional and structural, was emphasized. In three additional fatal cases investigated by Ferraro,[20] in which the survival periods (9 to 10½ days) were somewhat longer than usual, the changes already described were noted to be more profound and vascular alterations even more conspicuous.

Meanwhile, many observers had noted the similarity of the microscopic findings after insulin shock to those found in fatal cases of cerebral anoxia. This comparison was quite comprehensively evaluated on the basis of six fatal cases studied by Lawrence et al.,[21] who also called attention to the similar distribution of the lesions in the brain in the two conditions. Malamud[22] observed the occurrence of "pseudolaminar" distribution of cortical cell loss, at times associated with status spongiosus. He noted with others before him the tendency to affect Somer's section of the hippocampus.[11,20] All these changes—neuronal, interstitial, and vascular—have been summed up in Spencer's excellent review of the subject.[23]

But all of these lesions, both gross and microscopic, were essentially acute affairs,

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most of them less than a week old.* Yet in the literature there occasionally appeared reports of persons who had survived for weeks, or even months, usually with profound mental deterioration presumed to be of an organic nature. Cases in this category have been collected in a survey of the subject by Greer.[29] Unfortunately, no autopsies were done in this group of cases, so that even to the present time no information has been available as to the nature of the ultimate residual changes in the brain. It is for this reason that a report of the cases forming the basis of this study is considered to be of particular value.

Report of Cases

CASE 1.—*Woman of 31, a known diabetic, found in coma. Extremely low blood sugar found on emergency blood sugar examination. Only minimal clinical improvement. Development of diffuse motor signs. Death in cachectic state after 137 days. Autopsy: widespread cortical necrosis and degenerative changes in the corpus striatum, suggestive of cerebral anoxia.*

A white woman, aged 31, was admitted to the Los Angeles County Hospital on July 3, 1955, in a comatose state. Her husband had left her that morning in apparent good health, but on his return, at 9 o'clock in the evening, he found her in coma. An empty ½ pt. vodka bottle was lying nearby. It was learned that she had been examined one year before in another hospital, where a diagnosis of diabetes mellitus, chronic alcoholism, severe anxiety state, and pancreatic calcinosis had been made. The patient had been on a daily dosage of 27 units of isophane insulin. A month before admission she was found to have a fasting blood sugar of 197 mg. per 100 cc. A glucose tolerance curve was done, and at the end of one hour the glucose level was 490 mg. per 100 cc., and at the end of three hours it was still 487 mg.

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* It would take the reader too far afield to review the many valuable articles dealing with the experimental demonstration of the architectural and cellular changes in the brain resulting from insulin shock. The articles by Weil et al.,[21] Yannet,[22] Finley and Brenner,[26] Töbel and Maier,[27] and the unusually comprehensive monograph of Lorentzen[30] are to be recommended to interested students of this phase of the problem. These experimental studies are in essential agreement with the findings in human cases of hyperinsulinism.

On admission the patient was found to be deeply comatose, with the odor of alcohol on her breath. Because the blood sugar level was 24 mg. per 100 cc., the blood potassium 4.6 mg. per 100 cc. and the CO_2 26 vol.% the patient was sent to the diabetic ward for immediate attention.† She was given orange juice by Levin tube. An emergency tracheotomy was done because of excessive bronchial secretions, presumed to be the cause of cyanosis. The pulse rate was 100 per minute; the blood pressure, 120 systolic and 70 diastolic. Otherwise, the patient was physiologically normal. Neurologically, there was found a generalized muscular flaccidity, with marked hyporeflexia. A bilateral Babinski sign was elicited.

In the next few days the patient seemed to be more responsive to external stimuli, the coma being somewhat less deep. Sugar began to spill over in the urine, and the blood sugar was found to be 362 mg. per 100 cc. The CO_2 tension remained at 26 vol.%, however. The blood potassium was reported as 3.8 mg. per 100 cc.

The patient remained without change for some weeks. Daily sweats associated with hyperemia were noted. She continued to be deeply stuporous, responding little, if any at all, to painful stimuli. She did open her eyes if the limbs were moved to any appreciable extent but made no outcry and was evidently completely out of contact with her environment. The left pupil remained larger than the right. The deep reflexes were generally spastic, and pathological toe signs were elicited.

The patient began to lose weight and developed abscesses of the subcutaneous tissues, as well as many decubitus ulcers. Death came on Nov. 17, 1955, or 137 days after the hypoglycemic episode, as a result of bronchopneumonia and inanition.

A general autopsy was done on Nov. 18, by Dr. Roy George, resident pathologist, who found, in addition to the profound loss of weight and multiple decubitus ulcers, a flexion contracture of the extremities, minimal atherosclerosis, congestion and edema of the lungs, and calcareous deposits in the pancreatic lobules. Death was considered to be due to cerebral degeneration incident to hypoglycemia (insulin shock). The brain was submitted to the Cajal Laboratory for detailed examination after further fixation.

Before fixation the brain weighed 930 gm. It appeared to be definitely smaller than average.

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† Those who have had extensive clinical experience with hypoglycemia are well aware that it is not the quantitative estimation of blood sugar alone which indicates the actual state of the organism or the severity of potential damage to the brain. In this case, the one emergency blood sugar reading here referred to is at best only confirmation of the hypoglycemic state.
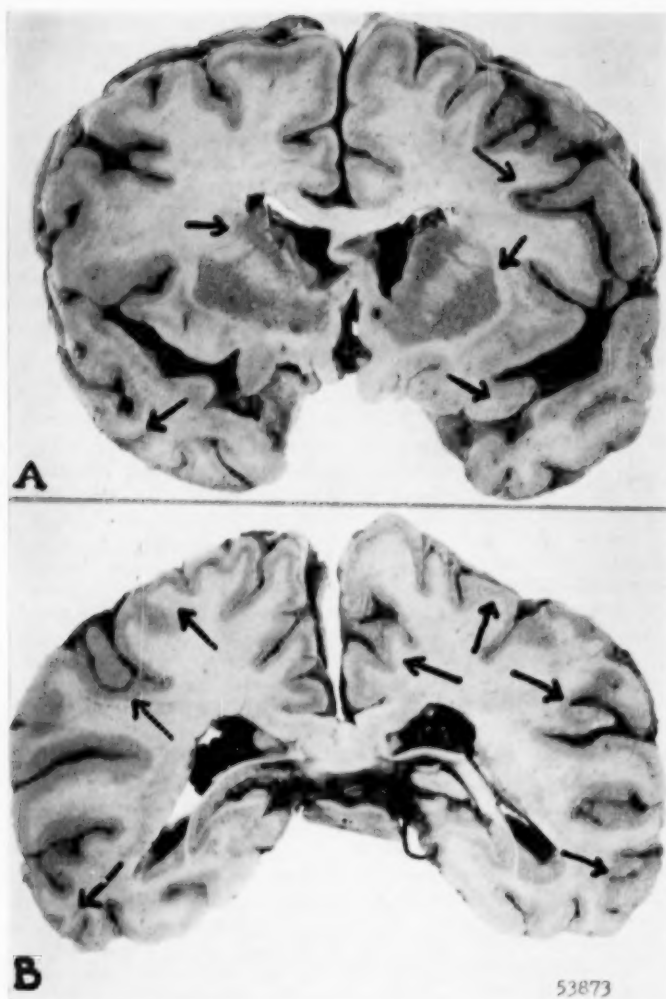
Fig. 1 (Case 1).— Coronal sections through the cerebral hemispheres in case of prolonged survival (137 days) in insulin shock. *A*, level of anterior limb of internal capsule, showing irregular cortical softening and of caudate nucleus and putamen (corpus striatum). *B*, level of splenium of corpus callosum, showing widespread cortical softening of the parietal and temporal lobes.

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The convolutions of the cerebral hemispheres showed an irregular atrophy, most conspicuous over the central areas. In addition, multiple areas of cortical softening were noted, the larger foci being found on the dorsolateral aspect of the left parietal region (Fig. 1). The cerebellum likewise appeared smaller than usual, but no foci of actual softening could be delineated.

The cerebral hemispheres were cut in a series of coronal sections. Practically all sections disclosed an advanced degree of cortical softening, a change most marked on the dorsolateral aspects of the hemispheres. This change was particularly severe in the frontal and parietal cortex, although subsequent sections indicated that the degeneration also extended into the temporal lobe, to involve all but the hippocampal gyrus. In addition, practically the entire corpus striatum (caudate nucleus and putamen) of both sides was softened and granular in appearance. The globus pallidus and optic thalamus were not materially affected. The lateral ventricles were symmetrically dilated, but the cerebral centrum, brain stem, and cerebellum were not grossly changed.

Sections were made from blocks from the cerebral cortex and basal ganglia and stained with hematoxylin and eosin or impregnated according to the reduced-silver, gold-sublimate (gold chloride-mercury bichloride), and Perdrau methods.
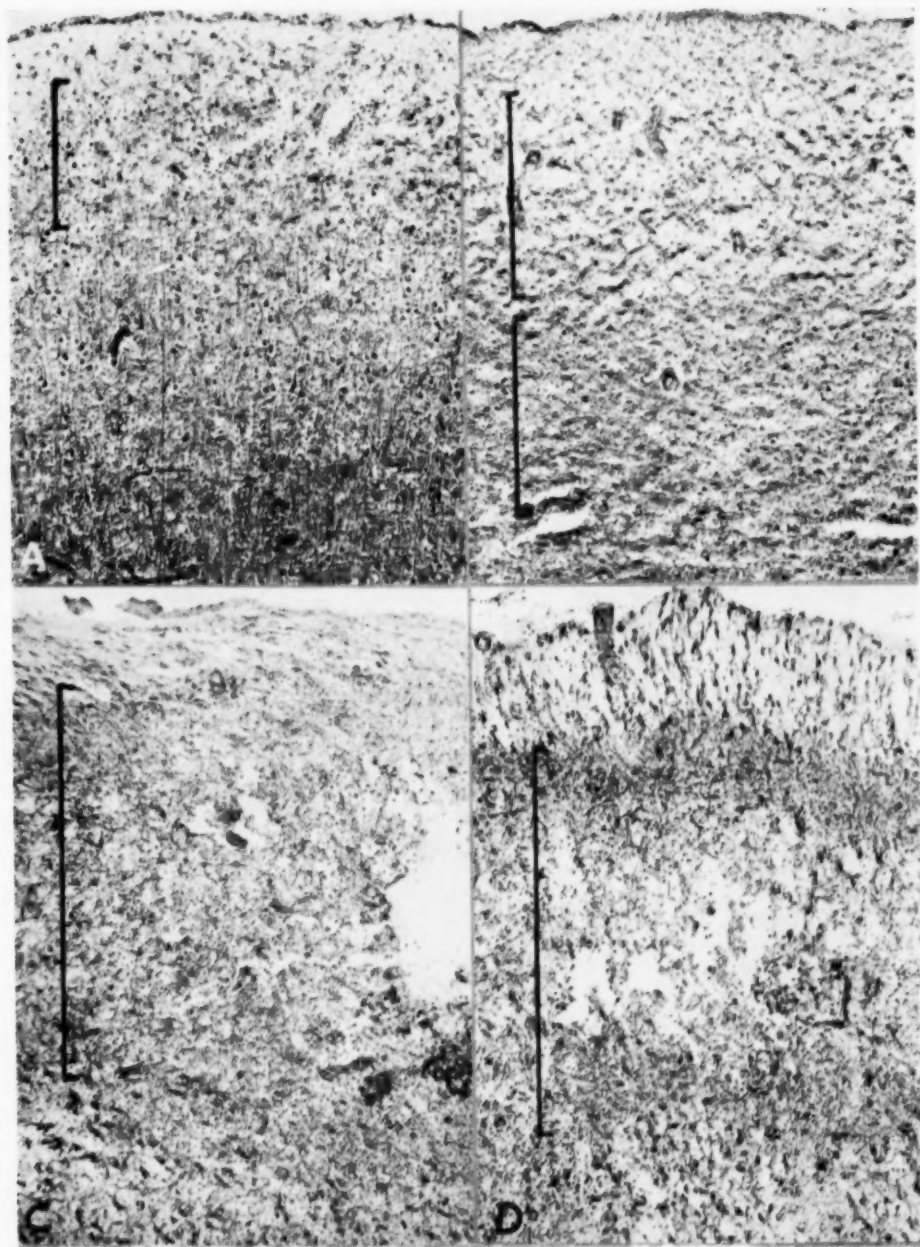
Fig. 2 (Case 1).—Cerebral cortical changes after insulin shock. Low-power magnification of section from the cerebral cortex, showing variable degrees of cortical degeneration. Reduced-silver method; reduced to 94% of mag. ×70. *A*, essential alterations are found in superficial laminae, whereas cell loss in cortex is spotty. *B*, architectural changes in upper and intermediate laminae, while deeper layers have suffered extensive loss of nerve cells. *C*, increased friability of all cortical layers except the most superficial (noncellular) and deepest ones. *D*, total intermediate laminar necrosis with superficial and deep zone of gliosis.

Courville
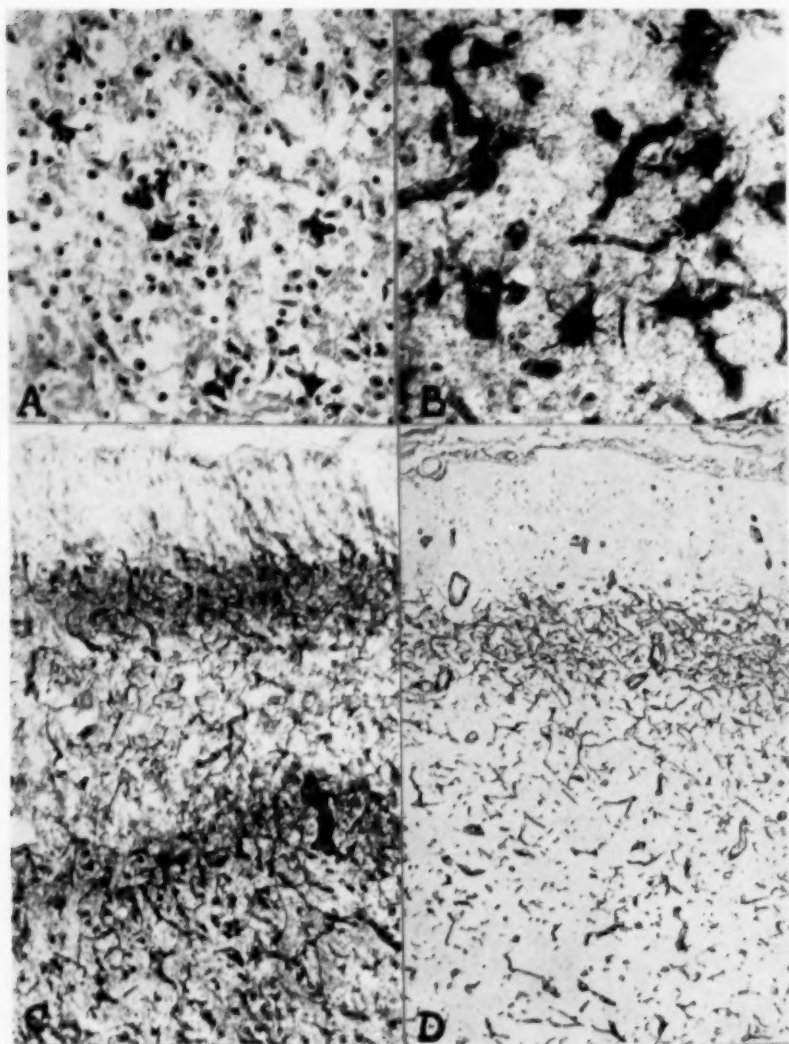
Fig. 3 (Case 1).—Cerebral cortical changes after insulin shock. *A*, "calcification" (ferrugination) in pyramidal nerve cells in partially softened cortex. Hematoxylin and eosin; × 275. *B*, reactive glia bordering zone of laminar necrosis. Gold-sublimate method; × 250. *C*, superficial and deep zones of glial reaction at margin of necrotic zone. Gold-sublimate method; × 70. *D*, zone of reticulin proliferation in superficial cortical laminae (Lamina III) in cortex otherwise showing only minor alterations (Fig. 2*A*). Perdrau method; × 70.

A survey of the cortical sections indicated a wide variety in degree of architectural change (Fig. 2*A* to *D*). The leptomeninges were generally thickened, due to proliferation of their fibrous elements. In sections that appeared normal to the unaided eye, there were found wide zones of status spongiosus, with loosening of the interstitial tissues. At times a double zone of necrosis was present. The superficial and deep layers were usually spared but presented a degree of gliosis. These zones of status spongiosus were often observed to be continuous with zones of laminar scarring and necrosis. In such zones the nerve cells had largely disappeared, although a few relics encrusted with iron (ferrugination) were still evident (Fig. 3*A*). The astrocytes in these zones were proliferated and undergoing hyaline change, forming a diffuse glial scar. These changes

were particularly evident in the subpial glial layer, but were also observed beneath the zone of necrosis (Fig. 3*B* and *C*).

The more advanced changes usually occurred in the deep cortex bordering the sulci, rather than in its exposed portion. The degree of density of the scar in the intermediate cortical zones varied widely, from a loose, friable band, which appeared badly broken up, to a closely knit glial scar with a moderate increase in number of hyalinized astrocytes.

The effect of laminar necrosis on the population of nerve cells was best shown in the reduced-silver preparations. In all of the areas studied, the intermediate cortical zones were practically devoid of pyramidal nerve cells. Only faint shadows, in which the cell body was observed to contain only fine argentophilic granules, could be seen. In the deep cortical zone below the zone of loose friability, status spongiosus, or actual necrosis, a small number of nerve cells could be made out. Under higher magnifications, however, faint outlines of nerve cells in clusters could also be seen in better-preserved areas. Even here the cell processes were deformed and blunted. Either the cell body was devoid of argentophilic material, or this substance was present in the form of coarse or fine granules or agglutinations of individual particles. In this zone an active proliferation of astrocytes was taking place.

The amount of endothelial proliferation leading to the formation of new capillaries was not remarkable in this case. Nevertheless, in the Perdrau preparations the presence of a well-defined superficial zone of vascularity (less often with a narrow, less vascular zone in the deeper cortex) was clearly evident. The prominence of this zone was due to an active proliferation of reticulin, rather than to actual increase in blood vessels. This material formed a dense network in the superficial layers of the cortex, less often in the deeper layers as well (Fig. 3*D*).

Sections from the lenticular nucleus stained routinely presented a definite pallor in the putamen and globus pallidus, evident even to the unaided eye. Under low magnifications, the tissues appeared to be friable and irregularly segmented in some areas. In others a loose glial scar had formed. In still others actual softening had taken place, with infiltration of numerous compound granular corpuscles. The endothelium of the blood vessels showed little tendency to proliferation, but Perdrau preparations disclosed areas in which increased numbers of capillaries formed a network of reticulin in some of these foci.

A reduced-silver preparation indicated that most of the nerve cells in the lenticular nucleus were also seriously damaged. The intracellular argentophilic material was reduced to a narrow border of granules about the nucleus, while the cell processes were short and fragmented. The remaining parenchymatous elements were overshadowed by proliferation of astrocytes undergoing hyalinization.

An unusual deposition of iron-calcium deposits was seen in some foci. In addition to the usual nodular concretions seen in the walls or environs of some of the small arterioles, small collections of granules of deeply staining material were observed. The significance of these collections is not clear, but the accumulation of groups of individual granules suggests the deposition of iron in a cluster of decadent nerve cells.

Comment.—In this instance a profound degree of insulin shock (the blood sugar being reduced to 24 mg. per 100 cc.) was evidently reinforced by the action of alcohol (also acting as a histotoxic-anoxic agent) to produce profound damage to the cerebral cortex and corpus striatum. A prolonged survival period in a vegetative state permitted a full development of widespread laminar cortical necrosis. The structural and cellular alterations were essentially the same as are found as residuals in cases of severe anoxia from various causes after any extended period of survival. This finding suggests per se some close similarity between the two processes.

CASE 2—*Coma from overdose of insulin administered in the treatment of diabetes mellitus. Persistent vegetative state for 86 days, with mild fluctuations in temperature. Development of "decerebrate" rigidity. Autopsy: terminal bronchopneumonia; diffuse cortical softening with necrotic changes in corpus striatum.*

A Negro woman, aged 32, had been seen in the hospital on Feb. 20, 1955, having been admitted because of nausea and vomiting, followed by dehydration of unknown etiology. A history of alcoholism was elicited. She was found to have diabetes mellitus and syphilis. She was discharged to the outpatient clinic on March 2, 1955, for routine treatment. Through some misunderstanding of instructions, on March 3 she gave herself three subcutaneous injections of 40 units of isophane insulin, instead of one. She complained of feeling somewhat dizzy after the third injection. She was found unconscious about seven hours later by her sister, who gave her still another injection of 40 units of insulin on the mistaken assumption that the patient was in diabetic coma. She was then sent into the hospital for care.

Examination showed the patient to be a thin, but fairly well-developed, comatose Negro woman.

Her respirations were slowed to 6 to 8 per minute, being irregular and spasmodic. The skin was cold and covered with perspiration. The pulse was 80 per minute; the blood pressure, 65 systolic and 40 diastolic. A spontaneous rotatory nystagmus was noted. The pupils were equal, round, and regular, but reacted very sluggishly to light. Some froth exuded from the mouth. The neck was slightly resistant to flexion. Coarse rhonchi were heard over the chest. The heart tones were faint, but the rhythm was regular. The deep reflexes were universally hyperactive, and equivocal toe responses were elicited.

The urine was found to be free of sugar and acetone. The blood sugar was found to be 221 mg. per 100 cc.; the CO_2, 21 mEq/l. (normal 26-33 mEq/l.); the sodium, 139 mEq/l., and the potassium, 5.9 mEq/l.

In spite of energetic treatment, the patient failed to respond and remained in coma throughout her hospital stay. After a week the temperature curve became irregular, being marked by slight diurnal rises. The patient also developed generalized muscular rigidity. She remained in a vegetative state until the time of her death, on May 29, some 86 days after onset of insulin shock.

The autopsy was performed by Dr. Victor Cefalu, of the coroner's service, who submitted the brain to the Cajal Laboratory for further examination. The frontal cortex appeared to be somewhat atrophic for a person of her age. There was an obvious diffuse softening of the cerebral cortex of the temporal and parieto-occipital regions of both hemispheres, with only minor variations in the distribution on the two sides (Fig. 4A). The cortex of the medial aspect of both frontal lobes was also affected.

On coronal section of the separate hemispheres, the cortical gray matter was found to be selectively softened. The narrowed and granular cortical ribbon presented a faint yellowish-brown coloration and was sharply delineated from the underlying white matter. Small foci of hemorrhage could be distinguished in some areas (Fig. 4B). On the left side the caudate nucleus and putamen appeared to be brownish in color and granular in consistency. On the right side a small focus of necrosis was observed in the medial aspect of the globus pallidus. In the temporal lobe, where the cortical changes were most marked, secondary alterations in the white matter were also noted. The amygdaloid nucleus seemed to be specifically softened.

Sections through the brain stem and cerebellum disclosed no grossly evident changes.

A series of sections from the cerebral cortex and underlying centrum and the basal ganglia stained with hematoxylin and eosin and impreg-

Fig. 4 (Case 2).—Cortical and ganglionic softening after prolonged survival (86 days) in case of insulin shock. A, section through posterior limb of internal capsule, showing softening of cortex, caudate nucleus, and internal segment of globus pallidus. B, section through thalamus and midbrain, showing severe degree of cortical softening and focus of red softening in temporal cortex.
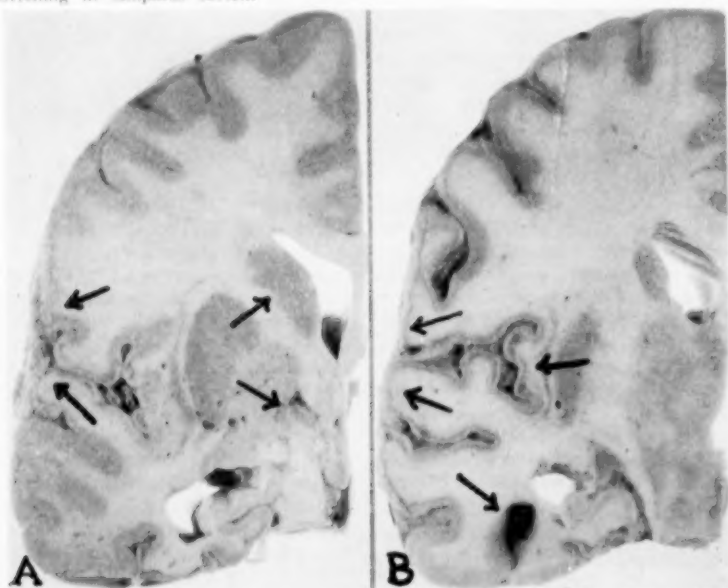
nated by the reduced-silver, gold-sublimate, and Perdrau methods were available for study. The cerebral cortex was altered by rather extensive laminar necrosis and foci of red softening. The leptomeninges showed a moderate degree of thickening, due to proliferation of the fibrous elements in all sections studied. Laminar necrosis was found in variable degrees, from one or more faintly visible layers of status spongiosus extending from the uppermost cellular layer almost to the underlying white matter to gross central necrosis (Fig. 5A). In these less altered areas the

Fig. 5 (Case 2).—Cerebral cortical changes incident to insulin shock. A, wide zone of laminar necrosis with almost total loss of nerve cells. Hematoxylin-eosin stain; ×70. B, section from less seriously altered portion of cortex. Superficial laminae show practically total loss of nerve cells, while in deeper layers small clusters of nerve cells can still be seen. Reduced-silver method; ×70. C, endothelial proliferation with early budding of capillaries in partially softened cortex. Hematoxylin-eosin stain; ×120. D, total cortical necrosis with superficial and deep zones of glial proliferation (A and B). Gold-sublimate method; ×75.

pyramidal nerve cells were considerably decreased in number, those that remained being seriously damaged. The loss of these cells often presented a laminar pattern (Fig. 5*B*). In some zones many of the nerve cells had undergone iron deposition, with their dark-purple cell bodies standing out in the scar. Some of these cells were completely enveloped by macrophages. In the more seriously affected zones, a band of hyalinized astrocytes had replaced the nerve cells. As a rule, some of the interstitial elements (perineuronal satellites) showed an increase in number, while others (astrocytes) in the deeper cortical layers showed hyaline change. In certain localized areas, endothelial proliferation was present, often leading to the formation of new capillaries (Fig. 5*C*).

In other zones with severer degrees of laminar necrosis, all traces of the normal disposition of the parenchymatous elements had disappeared. In fact, only rare examples of nerve cells were to be found. This zone of necrosed cortex had been more or less completely converted into a glial network of varying density in which the numbers of new-formed capillary vessels were found in proportion to the solidarity of the scar. The subpial astrocytes, as well as those in the deepest cortical layers, were multiplied and had undergone hyaline change (Fig. 5*D*). Collections of lymphocytes and phagocytic cells were found around some of the blood vessels.

Laminar necrosis was particularly well demonstrated in the reduced-silver preparations. In the less seriously altered portions of the cortex, entire laminae of nerve cells were found to be missing. In others, where a wide band of scar had replaced the intermediate layers of the cerebral cortex, with multiplication and hyalinization of the astrocytes, no nerve cells whatever persisted. The few remaining elements in the deep cortical layers were overwhelmed by the proliferation of astrocytes. In all nerve cells the argentophilic material was fragmented or granular. Over considerable stretches, destruction of the intermediate layers of the cortex had been so marked as to leave a grossly visible linear defect in the cortex, often with wide separation of the preserved superficial and deep zones. Particularly noteworthy in these areas was the advanced degree of gliosis, which extended deeply into the underlying white matter. This was shown in a particularly striking manner in the gold-sublimate preparations.

The foci of red softening were observed either as isolated lesions or contiguous to areas of laminar necrosis (Fig. 6*A* and *B*). These focal hemorrhages apparently occurred within areas of softening, as is suggested by the fact that the regional tissue was filled with new-formed blood vessels (Fig. 6*C*) and zones of cortical tissue undergoing liquefaction, containing compound

granular corpuscles. The red cells in these foci were observed to be undergoing variable degrees of degeneration, the best preserved being found at the periphery of the effusion. Particularly striking were the perivascular collections of lymphocytes in regional meninges and bordering cortex. Deep to the hemorrhages, the perivascular spaces were distended with phagocytes laden with brownish (hematogenous) pigment (Fig. 6*B*). Granules of this pigment were also found in the walls of regional blood vessels. The surrounding interstitial tissues contained many large hyalinized, and often multinucleated, astrocytes.

Routine sections through the lenticular nucleus showed a generalized looseness of the tissues with severe changes in the large nerve cells and disappearance of many of the small ones. In some areas foci of actual softening had taken place (Fig. 6*D*). Early proliferation of astrocytes, some of which were undergoing hyaline change, and collections of lymphocytes about the larger blood vessels were also noted (Fig. 6*E*). Some smaller vessels contained small calcospherites, while larger ones were marked by rings of iron and/or calcium (Fig. 6*F*). Foci of endothelial proliferation leading to new capillary formation and formation of a loose glial scar were also noted. In these areas numerous compound granular corpuscles, either loose in the defect or collected above regional blood vessels, were conspicuous.

Comment.—As in the first case, profound degrees of cortical and striatal change occurred as a consequence of an accidental overdosage of insulin. The patient had self-administered three instead of one injection of this substance. After she had lapsed into an unconscious state, her sister gave her a fourth injection on the assumption that her coma was of diabetic origin. In addition to the variable degrees of laminar cortical change, focal hemorrhages were observed in the sections of the brain, as have been occasionally reported by others. The character and degree of cortical and ganglionic changes again resemble those found in persons who survive for a prolonged interval a severe degree of cerebral anoxia.

Relation of Cerebral Changes in Insulin Shock to Cerebral Anoxia

A review of the reported changes in the brain in fatal cases of insulin shock suggests a striking similarity between such
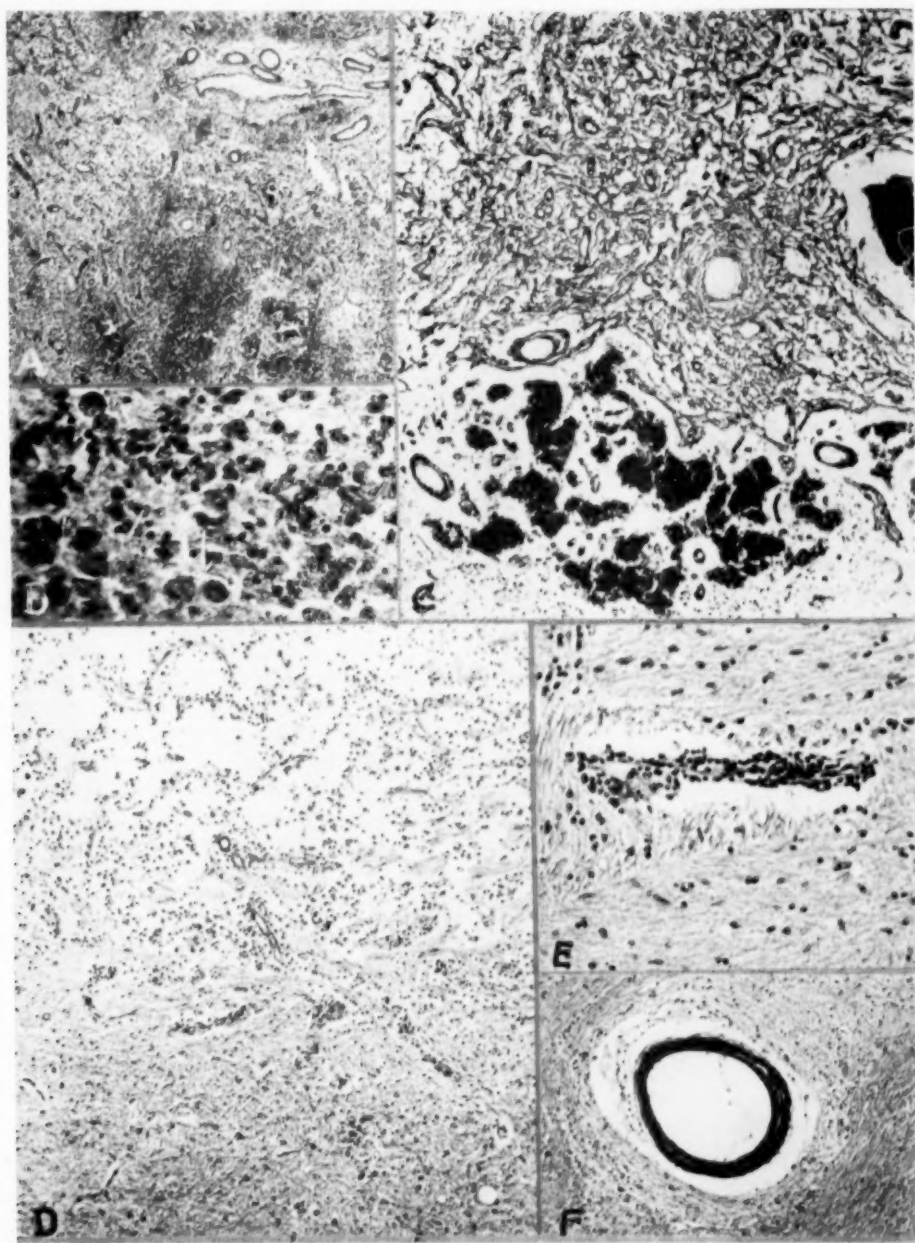
Fig. 6 (Case 2).—Cortical and ganglionic changes after insulin shock. *A*, section from cortical focus of red softening, showing effusion of red blood cells and capillary proliferation. Hematoxylin-eosin stain; reduced to 94% of mag. × 35. *B*, enlarged view, showing macrophages laden with hematogenous pigment; × 250. *C*, new-formed capillaries and diffuse network of reticulin from this area. Perdrau method; × 70. *D*, margin of focus of softening in lenticular nucleus, showing endothelial proliferation in regional tissues. Hematoxylin-eosin stain; × 70. *E*, perivascular accumulation of lymphocytes in lenticular nucleus. Hematoxylin-eosin stain; × 170. *F*, ring of calcium in tunica media of arteriole in lenticular nucleus. Hematoxylin-eosin stain; × 75.

alterations and those characteristic of cerebral anoxia. This is true of the acute changes found in persons who have died within a few hours, even though such changes consist essentially of a marked degree of congestion often associated with patchy subarachnoid hemorrhage and focal petechiae in the cerebral white matter.[9] If the patient survives for several days, the nerve cells of the cortex and basal ganglia (particularly the corpus striatum) give evidence of severe change.[10] As the survival period lengthens, laminar necrosis [11,12] and status spongiosus [22] become manifest. Ultimately the changes in the cerebral gray matter become quite profound and widespread,[13] resulting in clinical pictures of severe intellectual and motor deficits.[20] In the two cases with long survival periods here reported, the residual cortical and ganglionic damage is essentially identical with that found after cerebral anoxia incident to carbon monoxide,[30] nitrous oxide anesthesia,[31,32] mechanical strangulation,[7] cardiac standstill,[33] and shock.[34] It is pertinent therefore to inquire just how these changes take place in case of insulin poisoning. What relation, if any, do the effects of acute severe hypoglycemia bear to oxygen want?

Effects of Insulin Shock on Cerebral Glucose Metabolism.—As early as 1924 Olmsted and Taylor [35] noted that the effects of insulin on the brain occurred with but little alteration of the oxygen saturations of blood in the cerebral circulation. Holmes [36] pointed out, more specifically, that large doses of insulin interfered with the utilization of oxygen by the cerebral gray matter. This was found to be accompanied by a marked decrease in both brain glycogen and free sugar.[37,38] Weil et al.,[24] as well as other investigators, concluded that the nerve cells of the brain were unable to utilize oxygen in the presence of large amounts of insulin. This is but another way of saying that insulin shock brings about a state of histiotoxic anoxia even in the presence of an abundance of oxygen.[25] Insulin evidently depletes the nerve cells of their contained glycogen, as well as reduces excessively any available free glucose. Under these circumstances, these cells cannot utilize oxygen in their metabolic processes, with consequent damage to their structure.‡ This basic principle seems to be true regardless of the mechanism by which hypoglycemia is produced. It is operative in cases of hyperinsulinism resulting from pancreatic islet adenomas as well as in instances of overdosage of insulin in therapy.[8,39,40]

The abnormal metabolic process produced by hyperinsulinism seems to account for the changes in the individual nerve cells of the cerebral cortex and corpus striatum which have been so often described in reported cases. But how can the architectural alterations be thus explained? It has already been assumed that profound vasomotor disturbances must intervene to account for these focal lesions.[6] This mechanism is obvious in cases of cerebral anoxia, not only because of severe degrees of congestion observed in acute cases but also because of the ultimate residual lesions which can be explained only on a vasospastic basis (i. e., focal cortical-subcortical softenings). It may be assumed, therefore, that anoxia produces these effects by its action on the nerve cells constituting the vasomotor center, which are especially vulnerable to oxygen want. It must be concluded, therefore, that the same mechanism is at work in severe degrees of hypoglycemia. In both types of disorder a generalized effect is manifested by widespread changes in the nerve cells of the cerebral cortex and basal ganglia, while a specific localized effect is

‡ This conclusion that the effects of hyperinsulinism on the brain constitute but another form of cerebral anoxia receives support from another quarter. It has long been recognized that one form of cerebral anoxia reinforces the effects of another already present. This is seen in cases of accentuation of cerebral anoxia by narcotic agents which act as histiotoxic substances.[41] In the same way, barbiturates reinforce the effects of insulin shock.[35,42,43] Similarly, insulin accentuates the action of recognized anoxic states.[44] Both patients here described were chronic alcoholics.

exerted on the cells of the vasomotor center. This mechanism is manifested not only by local ischemic effects incident to vasospastic action on the smaller cortical blood vessels but also by continuation and accentuation of these effects, whether anoxic or histiotoxic, as the case may be, on the cortex and basal ganglia.

Summary and Conclusions

This study is based upon the residual findings in the brain in two patients who experienced severe degrees of insulin shock through overdosage. A patient thus injured may survive sufficiently long for the changes in the cerebral gray matter to attain a chronic stage. Extensive laminar necrosis of the cortex and destruction of the corpus striatum were present in both cases here reported, as well as diffuse cellular damage in less severely injured zones. These changes, both cellular and architectural, are identical with those alterations residual to severe degrees of cerebral anoxia in cases of carbon monoxide poisoning, nitrous oxide anesthesia, mechanical strangulation, cardiac standstill, and prolonged shock. These cases therefore lend support to the theory that insulin shock is but another form (histiotoxic) of cerebral anoxia, with respect to both its general cellular effects and its secondary vasomotor dysfunction.

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Brain Tumor Depth Determination by Electrographic Recordings During Sleep

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Our first interest in the study of the sleep-state electroencephalographic recordings in brain tumors was stimulated by the hope of improving the surface localization found in the waking-state EEG and of discovering a hidden focus when the waking-state EEG was indefinite. These hopes, except in an occasional case, were not realized.[1] However, as noted by Grossman et al.,[2] the capricious behavior of the slow-wave focus in the waking state when the brain tumor patient went to sleep became intriguing and demanded an explanation. Grossman et al. found that the delta focus tended to persist in sleep when the patient had seizure phenomena; although this finding was in accord with the data previously published,[1] there were too many exceptions for this to be the only crucial factor. Hence we were moved to study the problem more closely and to attempt a correlation between the actual operative findings and the characteristics of the waking- and sleep-state EEG records.

Method

Patients chosen for this study were those with essentially unilateral supratentorial tumors on whom a satisfactory EEG in both the waking and the sleep state was obtained. Midline or nearly uniformly bilateral (usually butterfly-type) tumors were excluded, since these tumors usually had non-focal abnormalities, or occasionally no abnormalities, in their EEG's. Comatose patients on whom no waking state EEG's could be obtained, as well as disturbed patients who could not be sedated for sleep, were excluded. All records were taken on an eight-channel Model IIIA Grass electroencephalograph. Fifteen scalp electrodes, covering

the frontal, central, parietal, occipital, anterior temporal, midtemporal, and posterior temporal areas of each hemisphere and the vertex, and two ear-lobe electrodes were used. Runs of both scalp-to-scalp and scalp-to-ear linkages were employed in the waking and the sleeping state. When deep lesions were suspected, pharyngeal (nasal) leads were used. Sleep occurred naturally (36 patients) or was induced by methylparafynol (Dormison) (55 patients) and occasionally by secobarbital (Seconal) (9 patients).

The EEG records were classified according to the change in the slow-wave focus when the subject went to sleep. It was sometimes difficult, owing to the complete distortion of the EEG patterning in some cases, to decide what electrically constituted a sleep pattern. There was, in the deeper stage of sleep, a general tendency of focal abnormalities to be less pronounced. Nevertheless, records were grouped into three broad categories: (A) those in which the slow-wave focus of the waking-state EEG persisted or occasionally increased in sleep, (B) those in which, in addition, there was distortion—usually suppression—of the sleep spindles and fast activity on the side of the focus and lesion, and (C) those in which the waking-state focus was obscured or disappeared entirely in sleep. Within these categories, notations of the waking-state EEG characteristics were made, i. e., whether the dysfunction was primarily in the 1 to 3 cps (delta) range or in the 4 to 7 cps (theta) range, and whether it was chiefly focal, as opposed to considerable bilateral representation. Whenever pharyngeal leads were used and whenever paroxysmal slow activity was encountered, these findings were recorded.

Tumors, on the basis of the pathology reports, were grouped into gliogenous, meningiomatous, and other types. The main clinical features in each case were noted. The neurosurgeon then supplied the crucial data regarding the size, exact location, and depth of the most superficial part of the tumors in relation to the convexity and the condition of the convexity cortex overlying the tumors, confirmed at operation or occasionally at autopsy. In gliogenous tumors, where at times the line of cleavage between normal and neoplastic tissue was indefinite, the depth was determined by the gross

appearance of the brain and the tumor. The consistency of the overlying brain was compared with that of the tumor and the line of demarcation estimated. No effort was made to establish a line of demarcation histologically, but in the light of our findings future studies will be carried out with this criterion. Correlations then were made of the electroencephalographical, operative, and clinical findings.

Results

The types of tumors and their relation to EEG groupings are listed in Table 1.

TABLE 1.—*Tumor Morphology and EEG Group*

	Group A	Group B	Group C	Total
Gliogenous tumors				
Glioblastoma multiforme	11	15	7	33
Astrocytoma	8	7	5	20
Oligodendroma	2	1	2	5
Undifferentiated	1	0	1	2
Total	22	23	15	60
Meningiomatous tumors	6	8	5	19
Other types of tumors				
Metastatic carcinoma	5	1	2	8
Metastatic melanoma	0	3	0	3
Sarcoma	2	0	0	2
Granuloma	1	1	0	2
Hemangioma	0	0	2	2
Hodgkins disease	0	1	0	1
Lymphoma	0	0	1	1
Ependymoma	0	0	1	1
Papilloma, choroid plexus	0	0	1	1
Total	8	6	7	21
Grand total	36	37	27	100

The only significant finding was that the hemangiomas, papilloma, and ependymona (all were intraventricular) occurred only in Group C. The size of the tumor did not appear to be crucial; the majority were large—roughly 4 cm. in diameter or larger. There were slightly more moderate-sized tumors in Group C.

The only differential clinical features of note were that seizures were commonest in Group B and papilledema was commonest in Group A.

The most striking correlation found was between the depth of the tumor as found at operation and the type of electroencephalographic changes during sleep (Table 2). In Group A—where the delta focus persisted into sleep—there were 36 tumors which in all instances were 3 cm. or less from the convexity cortex of the brain. Counting a surface tumor as at zero distance, the average depth from the convexity cortex of the tumors in Group A was 1.3 cm.; gliomas tended to be the deepest (1.5 cm.) and meningiomas the most superficial (0.4 cm.). Almost as striking was the fact that in all but three instances inspection or palpation of the cortex, if the tumor was not already on the surface, gave evidence of the underlying tumor: The convolutions might have been widened, flattened, or discolored or abnormally soft, hard, or fluctuant. In Group B—where the delta focus persisted in sleep, together with distortion of sleep potentials—the 37 tumors involved were likewise in all instances 3 cm. or less from the convexity cortex of the brain. These, however, tended to be more superficial; the average distance from the convexity cortex was 0.8 cm. The gliomas tended to be deepest (average depth 1.1 cm.) and the meningiomas most superficial (average depth 0.1 cm.). In only two instances was the cortex normal to inspection and palpation. In Group C—where the focal characteristics of the waking-state EEG tended to disappear in sleep—there were 27 tumors which were in all instances 3 cm. or more from the convexity of the cortex; the average depth of these tumors was 4.8 cm. Here, however, the meningiomas, usually on the floor of the middle fossa, were deeper (average 5.4 cm.) than the gliomas (average 4.6 cm.). Striking, too, was the fact that the convexity of the cortex was usually normal in these cases and in all but five instances gave no suggestion of an underlying tumor.

Illustrative Cases

Illustrative cases in each tumor category of the three EEG groupings are as follows:

TABLE 2.—*Tumor Depth and EEG Group*

	Group A		Group B		Group C	
	Average, Cm.	Range, Cm.	Average, Cm.	Range, Cm.	Average, Cm.	Range, Cm.
Gliogenous	1.5	0-3	1.1	0-3	4.6	3-6
Meningiomatous	0.4	0-2.5	0.1	0-0.5	5.4	3-6
Other types	1.1	0-3	0.5	0-3	4.9	4-6
Average for all tumors	1.3		0.8		4.8	

GROUP A: CASE 1 (Fig. 1).—A 40-year-old woman had severe headaches and difficulty with memory for three weeks prior to admission. The only neurologic finding was bilateral papilledema. The EEG showed a right frontal delta focus, which persisted in light sleep induced by secobarbital. Ventriculography demonstrated a right frontal mass. At operation the right frontal convolutions were seen to be widened and flattened and felt hard. At a depth of 2 cm. a large glioblastoma multiforme was encountered.

L F - V
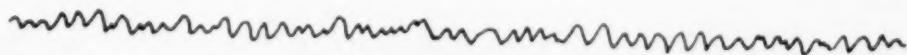
R F - V
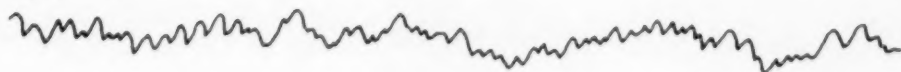
A W A K E
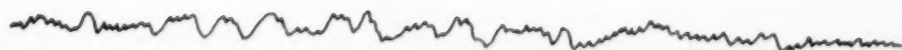
1 SECOND   50 uV

A S L E E P
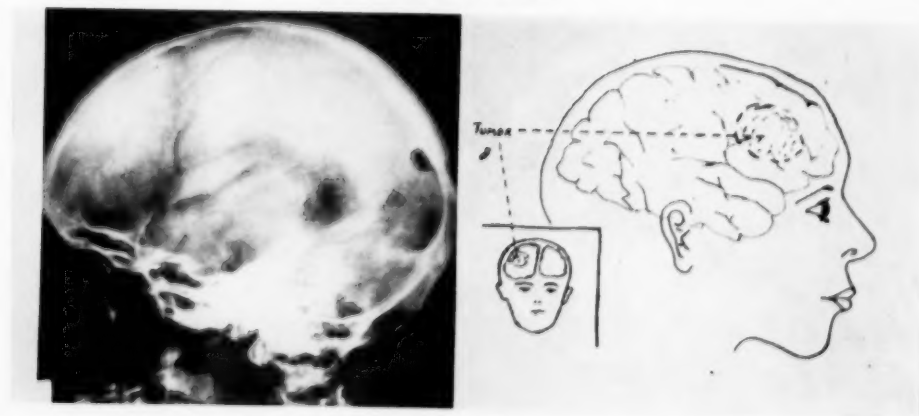
Figure 1

CASE 2 (Fig. 2).—A 31-year-old woman had a grand mal seizure two days before admission. Neurologic examination revealed bilateral papilledema and a slight weakness on the right. The EEG showed considerable bilateral theta activity, slightly more on the left, and maximal at the nasal leads; on sleep induced by methylparafynol, rhythmic notched 5 cps waves were seen in the left parieto-occipital leads. Ventriculography demonstrated a left parieto-occipital mass. At operation a large surface meningioma, close to the falx, was discovered in the left parieto-occipital area.
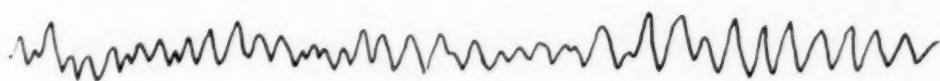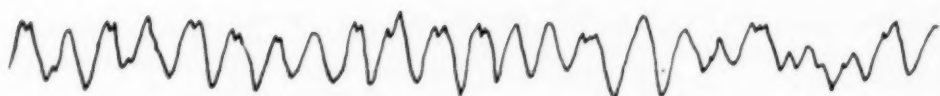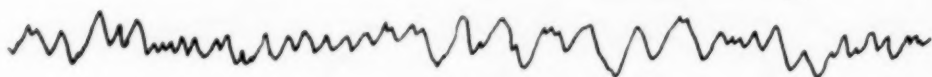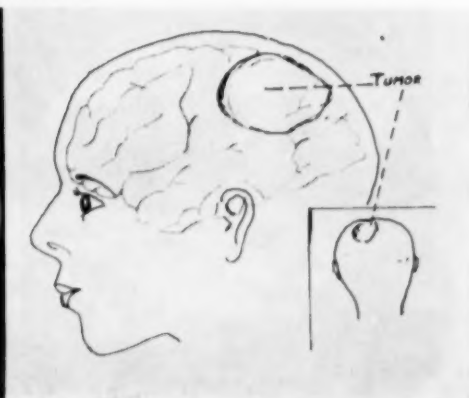
Figure 2

CASE 3 (Fig. 3).—A 43-year-old woman had a radical mastectomy 10 months prior to admission and for four months had left frontal headaches and diplopia. Neurologic examination revealed papilledema, right sixth nerve weakness, and mild right hemiparesis. The EEG showed a delta focus in the left temporal area; during methylparafynol-induced sleep the asymmetry remained. Ventriculography revealed a left temporoparietal mass. At operation a moderate-sized metastatic carcinoma was found on the surface of the lower third of the left temporal convolutions.

L ANT. T – V

R ANT. T – V

AWAKE

1 SECOND   50 u V

ASLEEP
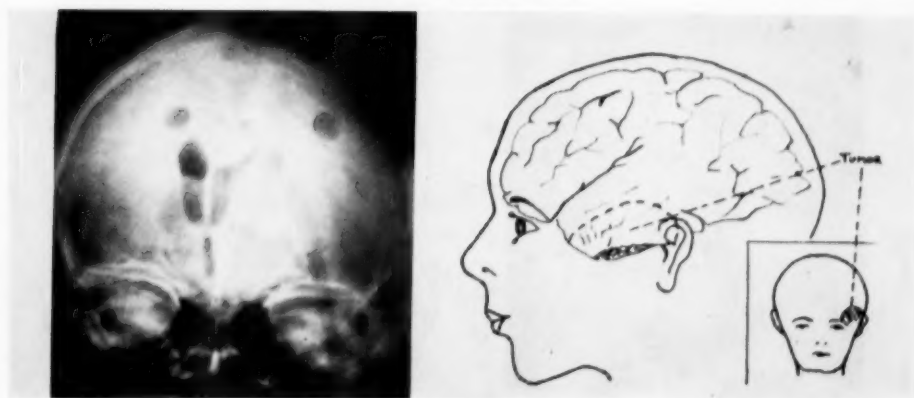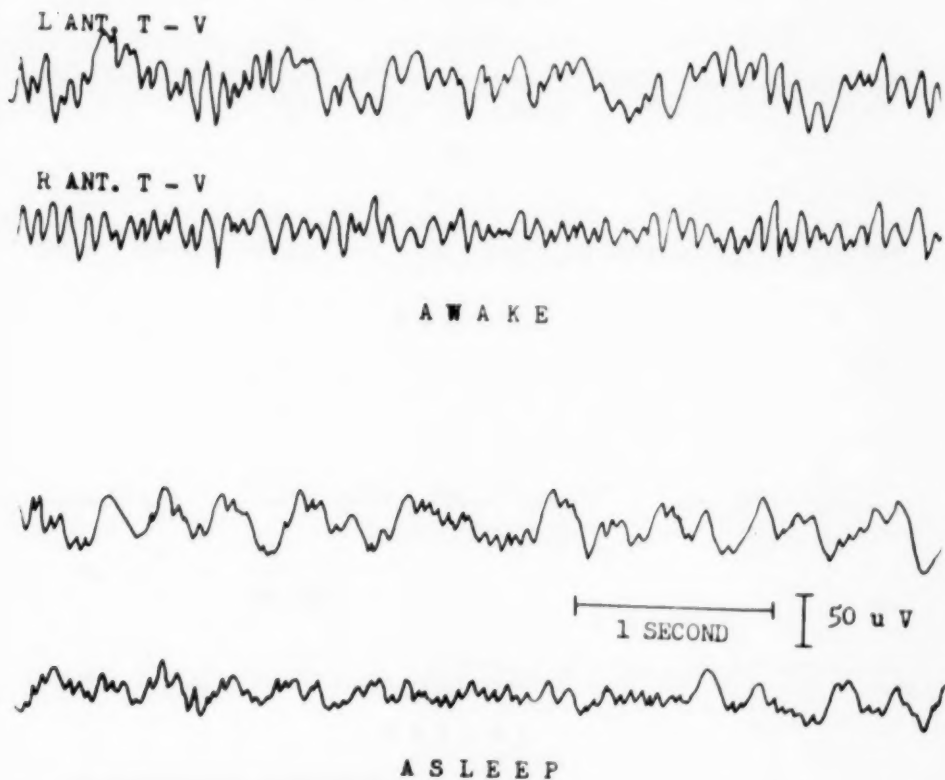
Figure 3

GROUP B: CASE 4 (Fig. 4).—A 30-year-old man had a series of four grand mal convulsions the day of admission to the hospital. The only neurologic sign was a right Babinski reflex. The EEG showed delta and theta activity, maximal in the left frontal area; during methyl-parafynol-induced sleep the focus persisted, together with suppression of sleep spindles and fast activity. Ventriculography revealed a left frontal mass. At operation the left frontal convulsions were found to be widened, flattened, and blanched; at a depth of 2 cm. a large astro-blastoma was encountered.

R F - R E
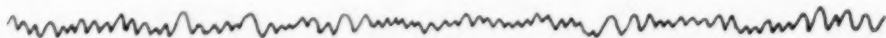
L F - L E

A W A K E

1 SECOND | 50 uV

A S L E E P
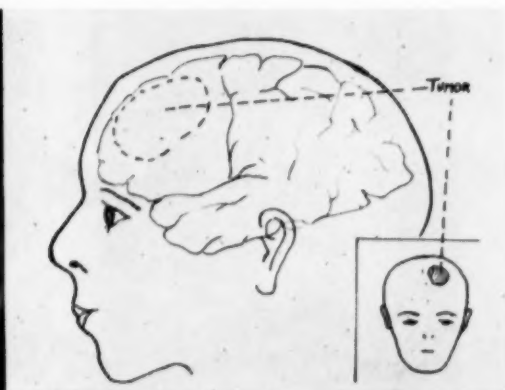
Figure 4

CASE 5 (Fig. 5).—A 52-year-old woman had several hospitalizations and courses of electro-shock therapy for endogenous depression over the six years preceding admission. For six months before admission she suffered with headaches and some memory deficit. Neurologic examination was negative. The EEG showed a moderate theta and delta focus in the right frontal region; on methylparafynol-induced sleep this focus persisted, together with depression of sleep spindles and fast activity. X-ray showed a right frontal density; ventriculography suggested a mass in the right frontal region. At operation a large surface meningioma, the size of an orange, was found in the right frontal region.
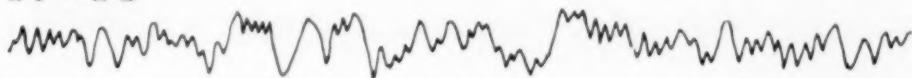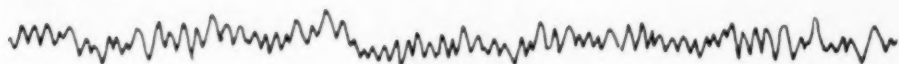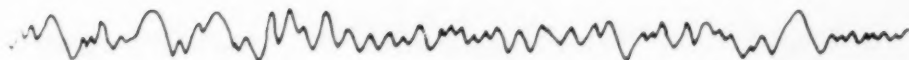
Figure 5

CASE 6 (Fig. 6).—A 38-year-old man had headaches and slight personality changes two months prior to admission. Five years previously he had had a small pigmented tumor removed from his back. Neurologic examination revealed bilateral papilledema and right pyramidal tract signs. The EEG showed a left frontal theta and delta focus; on methylparafynol-induced sleep the focus persisted, with suppression of sleep spindles and fast activity on the same side. Ventriculography demonstrated a left frontal mass. At operation a small part of a metastatic melanoma was visible on the surface of the left frontal lobe; most of the large tumor was at a depth of about 2 cm.
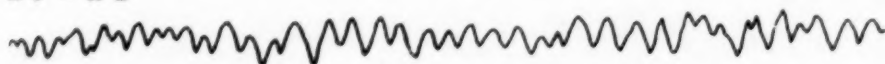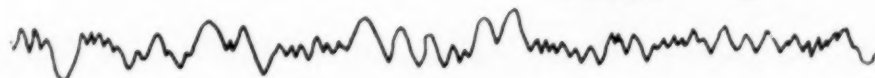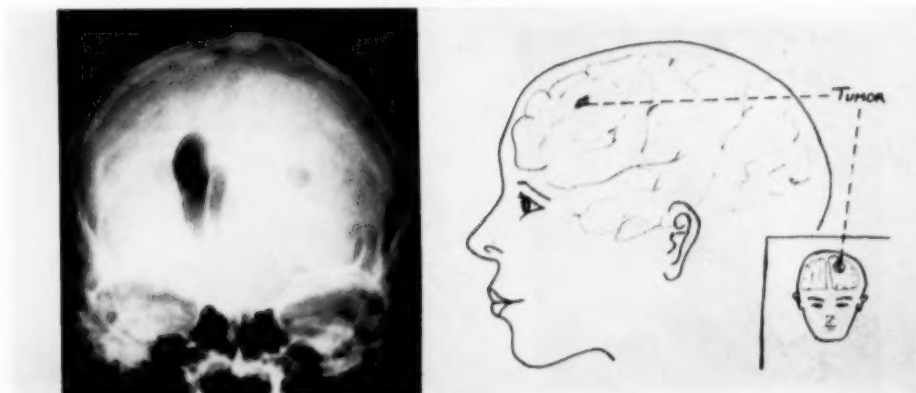
Figure 6

GROUP C: CASE 7 (Fig. 7).—A 49-year-old woman suffered with headaches for six weeks prior to admission. Neurologic examination revealed bilateral papilledema, bilateral external rectus palsy, and left central facial weakness. The EEG showed a right temporal theta and delta focus, which, on methylparafynol-induced sleep, tended to be obscured. Ventriculography indicated a right parietal mass lesion. At operation the cortex was normal; at a depth of 4 cm. in the right parietal lobe a large glioblastoma multiforme was encountered.
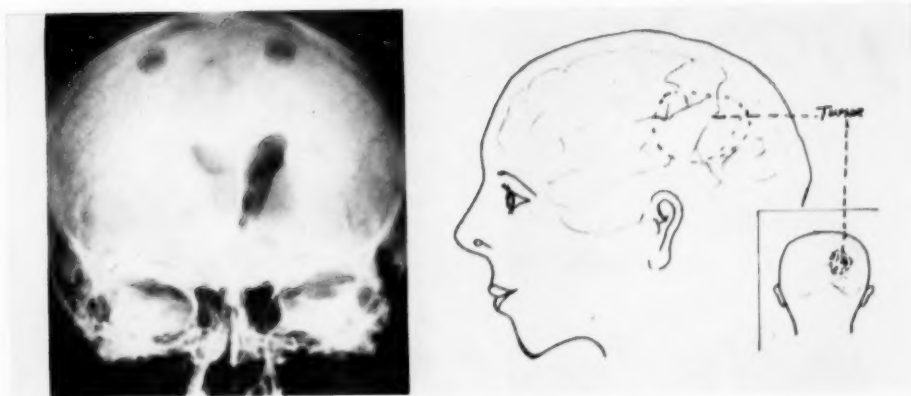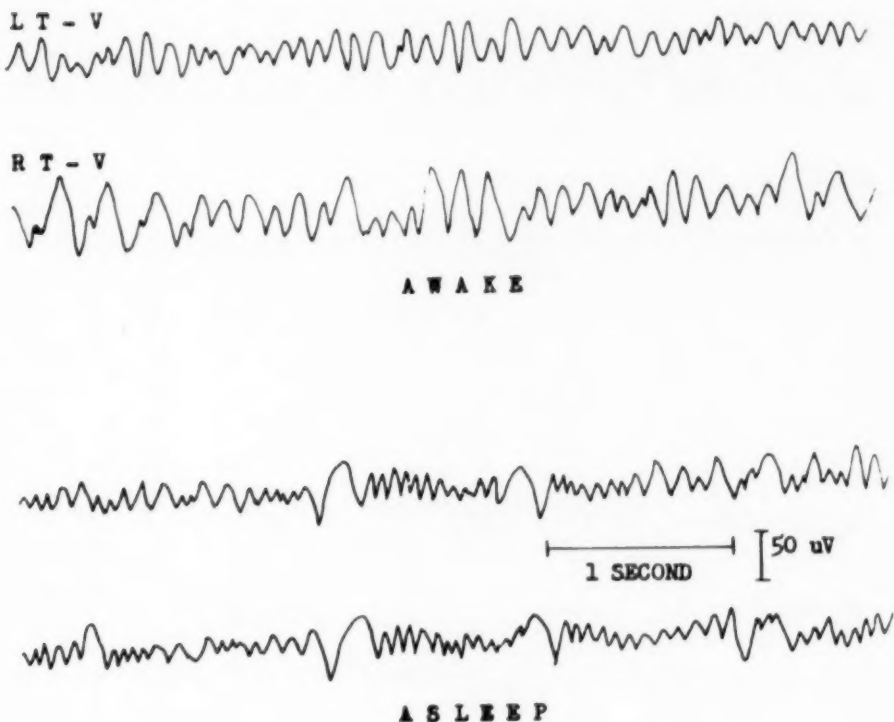
Figure 7

CASE 8 (Fig. 8).—A 40-year-old woman had six grand mal seizures over the 11 months prior to admission and for 6 months had noted gradual personality changes. Neurologic examination revealed bilateral papilledema. The EEG showed a moderate left temporal theta and delta focus, which on methylparafynol-induced sleep disappeared. Ventriculography suggested a mass in the left frontoparietal region. At operation the left temporal convolutions appeared normal, but on the floor of the middle fossa was a large meningioma compressing the temporal lobe upward.

L T - V

R T - V
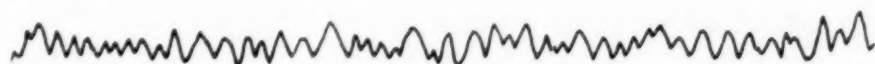
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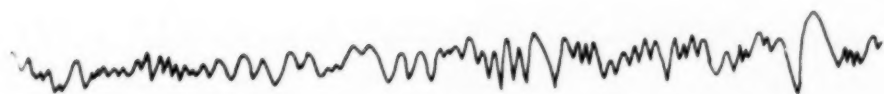
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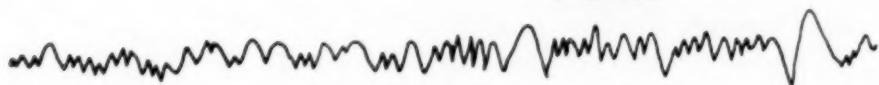
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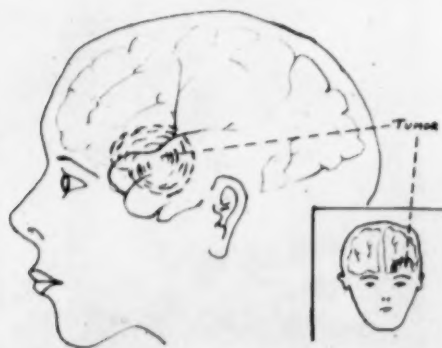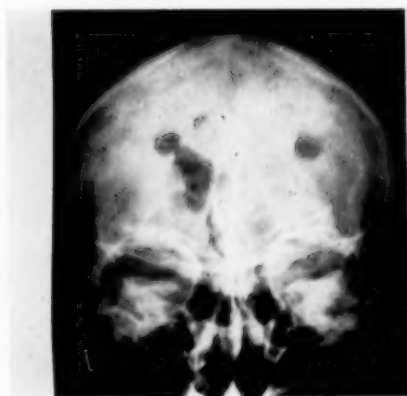
Figure 8

CASE 9 (Fig. 9).—A 13-year-old boy noted weakness on the left for two months prior to admission. Neurologic examination showed left spastic hemiparesis with the Babinski sign, clonus, and increased reflexes. The EEG showed generalized theta and delta activity, maximal in the right posterior temporo-occipital area; on secobarbital-induced sleep the focus disappeared. Pneumoencephalography showed a large tumor in the region of the pineal. At operation the cortex was found to be normal; on the floor of the posterior horn of the right lateral ventricle, at a depth of 5 cm. from the convexity cortex, there was a moderate-sized hemangioma.
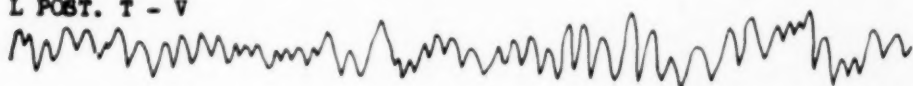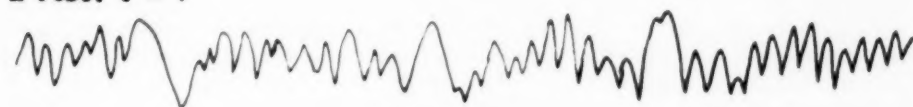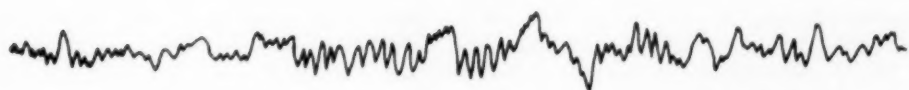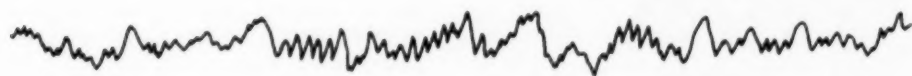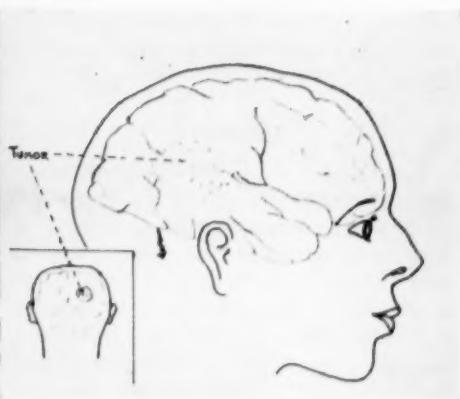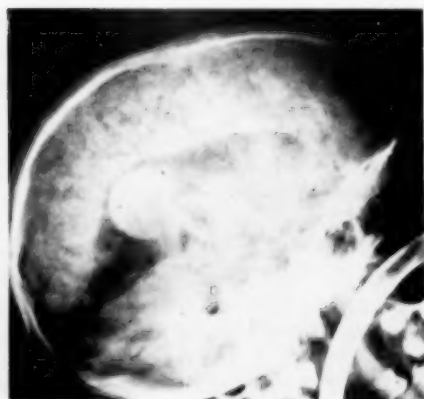
Figure 9

TABLE 3.—*Waking-State Characteristics and EEG Group*

		Focal Delta	Focal Theta	Considerable Bilat. Delta	Considerable Bilat. Theta	Slow Bursts in Addition	Nasal Localization
Group A							
Gliogenous	(22)	13	4	4	1	2	2
Meningiomatous	(6)	3	1	0	2	1	0
Other types	(8)	4	1	3	0	0	0
Total	(36)	20	6	7	3	3	2 (of 8)
Group B							
Gliogenous	(23)	14	2	4	3	3	2
Meningiomatous	(8)	2	4	0	2	3	1
Other types	(6)	4	1	1	0	0	0
Total	(37)	20	7	5	5	6	3 (of 9)
Group C							
Gliogenous	(15)	5	3	1	6	3	3
Meningiomatous	(5)	1	1	0	3	1	2
Other types	(7)	3	1	1	2	1	1
Total	(37)	9	5	2	11	5	6 (of 11)
All tumors							
Gliogenous	(60)	32	9	9	10	8	7
Meningiomatous	(19)	6	6	0	7	5	3
Other types	(21)	11	3	5	2	1	1
Total	(100)	49	18	14	19	14	11 (of 28)

Predominantly focal delta changes in the waking-state EEG's were seen in all groups, but less in Group C—33%, as compared with 55% (Table 3). Focal theta activity was approximately equal in all groups. Bilateral delta activity was commoner in the more superficial tumors—16%, as compared with 7% for Group C; this was found primarily in those large tumors that extended toward the depth or midline. On the other hand, bilateral theta activity was much commoner in the deep-tumor group (C)—41% as compared with 11%. Twenty-eight of the tumor cases were studied with pharyngeal leads. Proportionately more of those in Group C gave nasal-lead reversals (55%), as compared with Groups A and B (29%). Bursts of slow activity were uncommon (14 cases) and occurred slightly oftener in Group C (19%) than in Groups A and B (12%).

Comment

Waking-state EEG characteristics which have been utilized to indicate a deep-seated unilateral tumor are the amount of bilateral slow activity, particularly in the theta range,[3,4] the presence of a pharyngeal-lead localization,[5] and the tendency to paroxysmal slow activity.[6,7] The last feature, in our experience, applies more strictly to midline lesions, which were excluded from this study. As can be seen in Table 3, although burst activity was not a reliable indicator of the depth of a unilateral lesion, bilateral theta activity and pharyngeal-lead localization occurred more commonly in deep than in superficial tumors. However, they did not have the consistency that the sleep-state EEG's were able to demonstrate. Furthermore, there were occasions, particularly with lesions near the midline, such as parasagittal tumors, when the bilateral theta activity and nasal-lead reversals were misleading as to depth. Thus the sleep-state EEG, when compared with the waking state record, provided the most reliable electroencephalographic signs of the depth of a unilateral supratentorial tumor and has been utilized successfully to predict locations preoperatively.

Why this should occur is a matter of interest, though the ultimate explanation may not be known until the neural mechanism involved in the production of sleep-state potentials is more fully understood.[8-10] One fact is clear from this study: The recording of normal sleep-state patterns by scalp electroencephalography necessitates a relatively intact cortex, since the closer a tumor is to the cortex—and the more the cortex is pathologically affected—the more likely are the EEG patterns of sleep to be disrupted. This is, of course, equally true of the EEG in the waking state. However, it is apparent that the degree of disturbance

in the cortex that would lead to a disruption of waking-state patterns is less than the degree necessary to disrupt the sleep-state rhythms; it is not unusual to see a pathologically slow waking-state EEG (from a variety of causes) become "normal" in sleep. This could be anticipated on the basis of the more highly integrated functioning demanded during alertness, which is more easily interfered with by destructive processes than the lower level of functioning required during sleep. It is this differential, it is believed, which allowed for the prediction of tumor depth. On the other hand, it is well known that *discharging* epileptogenic foci are often more readily seen in sleep than in the waking state. It has been hypothesized that this is a release phenomenon when one is dealing with cortical epileptogenic lesions, since sleep may approximate physiologically the paroxysmal burst activity seen in isolated cortex preparations.[11-13] The integrated functioning of the waking state hence tends to inhibit the epileptogenic activity. This would be in line with the work of Grossman, who found that the potentially epileptogenic delta focus was more likely to persist into the sleep state. It is apparent that when a superficial destructive lesion is also epileptogenic, the two factors mentioned above will cooperate in sleep to make the focus more evident. However, when a deep destructive lesion is also epileptogenic, the two factors will be in opposition, and, should the epileptogenic factor prevail, it would contribute a possible source of error in the predictability of tumor depth by the method outlined.

Summary and Conclusions

Electroencephalograms of 100 unilateral supratentorial tumors were analyzed according to the changes seen electrically from the waking to the sleep state and were compared with operative findings. It was found that (1) tumors which showed a persistence of the slow-wave focus into sleep with suppression of sleep potentials were the most superficial with respect to the convexity of the brain, (2) tumors which showed only a persistence of the slow-wave focus were likewise superficial but deeper than the former, and that (3) tumors which showed a disappearance of the delta focus and a relative lack of distortion of sleep patterns were the deepest and were more than 3 cm. from the convexity cortex of the brain, which usually was grossly normal in appearance at operation. Thus, analysis of the electrographic changes from the waking to the sleep state provided a reliable indicator of the depth at which a tumor was encountered at operation. It is believed that this effect is produced by the fact that, while an intact cortex is necessary both for normal sleep and for waking-state EEG patterns, the degree of electroencephalographic dysfunction resulting from a destructive lesion is less pronounced during sleep that it is during the waking state.

269 S. 15th St. (3).

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Relationship Between Cerebral Vascularity and P^{32} Uptake

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It has been known from previous experiments[2] that various portions of the brain exchange radioactive phosphate with the plasma at greatly different rates. The fastest exchange was observed in the superficial layers of the cortex and in the ventricular lining. This was explained by the proximity of cerebrospinal fluid, which acted as an intermediary in the transport of P^{32} from plasma to brain. Nevertheless, the great number of capillaries in the cortex as compared with that in the white matter could not be disregarded as a factor contributing to the increased rate of phosphate exchange. It has also been considered[16] that the presence of blood in these capillaries misleadingly increases the P^{32} concentration of the tissue specimen in experiments of short duration when the specific activity of the blood is still considerably higher than that of the brain.

Material and Methods

The experiments were performed on 20 cats. A standard dose of 0.1 mc/kg. of body weight of P^{32} was injected intravenously. Thirty minutes to two hours later a trypan blue solution, containing 0.1 gm/kg. of body weight of the dye in 0.45% NaCl, was injected into a leg vein. Five to fifteen minutes after the injection of vital dye 150-350 cc. of an isotonic saline solution was injected rapidly into the previously exposed carotid arteries. Immediately after the perfusion the brain was removed. Blood sample for P^{32} determination was taken before the start of the trypan blue injection.

A second blood sample was taken just before the perfusion.

The administration of trypan blue served two purposes: 1. To check the efficacy of the perfusion. In case of satisfactory perfusion, the brain shows no blue staining on gross examination and under the microscope no dye is visible within the lumen of the cerebral capillaries. 2. To outline and define clearly small areas of the central nervous system, such as the medial and inferior portions of the hypothalamus and the area postrema. These areas have peculiar barrier properties. They stain with vital dyes but cannot be delineated clearly in unstained specimens.

The brains were deep-frozen after removal and the P^{32} concentration of their various portions determined by radioautography and by direct tissue counting. The choroid plexuses were isolated and removed from the brain for separate determination.

The results of this perfused series were compared with similar data obtained in cats without perfusion. For comparative purposes, the P^{32} concentration of various portions of the brain was computed to standard plasma P^{32} level.

It was found, by comparing the plasma P^{32} level before and after trypan blue injection, that this injection did not cause significant alteration in the amount of the isotope circulating in the blood stream. The difference between the plasma P^{32} concentration 10 and 20 minutes apart, and covering the vital dye injection, corresponded to the same percental difference in control P^{32} plasma curves.

Results

Effect of Perfusion.—The experimental data indicate that rapid perfusion fails to alter the rate of exchange between plasma and brain tissue. The amounts of P^{32} in various superficial and deep portions of the brain are identical in perfused and nonperfused brains. This again indicates that the presence of highly radioactive plasma in the cerebral blood vessels does not contribute
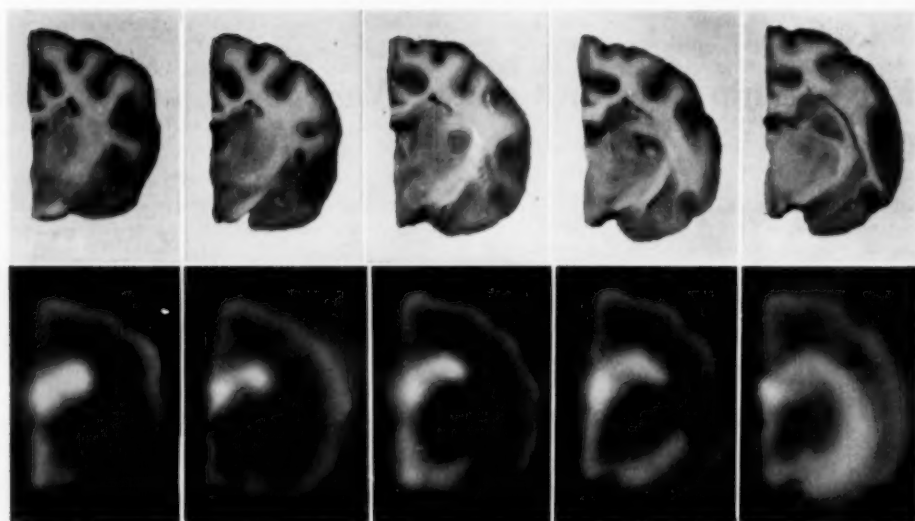
Fig. 1.—Cross sections of the left cerebral hemisphere with corresponding radioautographs prepared 2 hours and 30 minutes after intravenous injection of 0.4 mc. of P^{32}. Exposure time: 48 hours. The cerebral vessels were perfused with saline. P^{32} concentrates in the superficial layers of the cortex and in the ventricular lining (temporal horn) to the same extent. The rest of the brain contains only traces. The choroid plexus incorporates large amounts of the isotope.

materially to the values found in the tissue. Neither is there any density difference between perfused and control brains in comparable radioautographs (Figs. 1 and 2). The absolute P^{32} content, as well as its pattern of deposition in various layers, is not changed following perfusion. The most superficial layers of the cortex and the areas closest to the ventricles concentrate much more P^{32} than the regions which are situated farther away from cerebrospinal fluid spaces.

Table 1 summarizes the P^{32} concentration of superficial and deep portions of the brain

Fig. 2.—Cross sections of the left cerebral hemisphere with corresponding radioautographs prepared 2 hours and 10 minutes after intervenous injection of 0.4 mc. of P^{32}. Exposure time: 48 hours. The cerebral vessels were not perfused. No difference in concentration and pattern of deposit of P^{32} can be seen as compared with Figure 1.
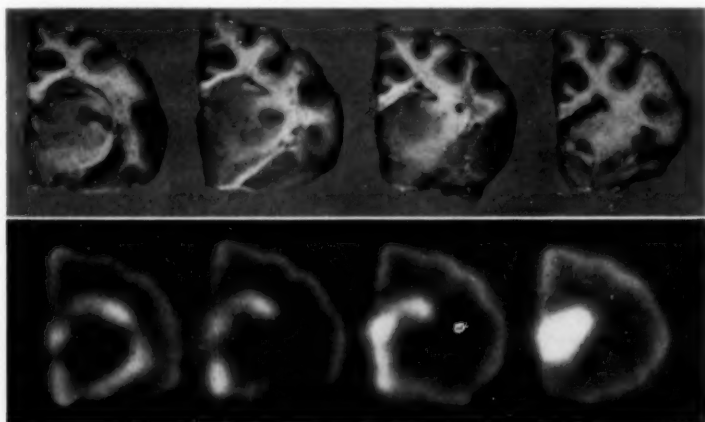
TABLE 1.—*P³² Content of Various Parts of Central Nervous System* *

| | A. Perfused Group | | |
Cat	Superficial Cortex	Deep White Matter	Choroid Plexus
34	3.5	0.1	36.5
36	3.8	0.1	44.3
39	6.2	0.2	....
41	3.1	0.0	....
47	6.5	....	39.0
49	7.8	0.6	36.4
67	3.6	0.0	20.6
71	3.0	0.1	24.0
Average	4.7	0.1	34.7
	B. Unperfused. Control Group		
14	5.0	0.1	49.0
42	4.6	0.2	75.4
76	3.2	0.4	43.5
82	6.4	0.1	67.8
108	4.9	0.0	35.0
Average	4.8	0.2	54.1

* P³² was injected two hours before death. Values are expressed in counts per minute per milligram of tissue and computed to a standard P³² plasma level (10.0).

in two groups of cats, two hours after administration of the isotope. One group had the cerebral vessels perfused; the other served as control. At the stage of two hours the relationship of phosphate contents of plasma, cerebrospinal fluid, and brain is fairly well established; yet the specific activity of the plasma is still greater than that of even the most active brain tissue. However, there is no difference in cerebral P³² concentration between the two groups.

The P³² content of the choroid plexus is reduced by perfusion. This seems to be most pronounced in experiments in which the perfusion was performed 30 minutes after injection, but there was a considerable variation in the values obtained at this early stage. The two groups of two-hour stage (Table 1) show that the P³² concentration of the choroid plexus in the perfusion group is 36% lower than that of the control group. Tubiana et al.,[14] in experiments using prolonged perfusion and Br⁸² as indicator, found a reduction of 19%-65% of the tracer content of perfused choroid plexus. The amount of P³² washed out from the choroid plexus by rapid perfusion corresponds to that stored in the plasma of this extremely vascular organ. It is certainly remarkable that much of its P³² is already so firmly incorporated that it cannot be mobilized.

Particular attention was paid to the P³² uptake of the area postrema. The area

postrema of cats is a V-shaped area along the edges of the lower part of the fossa rhomboidea, converging to the obex. It consists of an abundance of sinusoidal vessels embedded in a loose stroma and is distinctly colored by vital dyes, including trypan blue. It can be easily detected by its vital staining after the removal of the choroid plexus of the fourth ventricle. It always concentrates large amounts of P³², comparable to those found in the choroid plexus, as seen in radioautographs (Fig. 3). On direct tissue counting, however, I obtained usually lower values in the area postrema. This is probably caused by technical difficulties in isolating the area postrema from the neighboring tissues of the medulla, which contain 10-20 times less P³². Consequently, adherent particles of the medulla decrease the number of counts per unit weight.

For the same reason, it was impossible to evaluate the effect of perfusion on the P³² concentration of the area postrema. Direct, but not sufficiently accurate, counting indicated a slight reduction after perfusion. Radioautography, on the other hand, revealed no significant difference in perfused and in control brains.

Barrier Damage in Anesthesia Death.—Interesting abnormalities were found in the present experimental series and in past ex-

Fig. 3.—*A*: Axial section of fourth ventricle and medulla, revealing vitally stained area postrema (arrows). *B, C, D*: Corresponding radioautographs, showing P³² concentration in the area postrema from 30 minutes to 2 hours after injection of the isotope. Vascular perfusion. Exposure time: 48 hours.
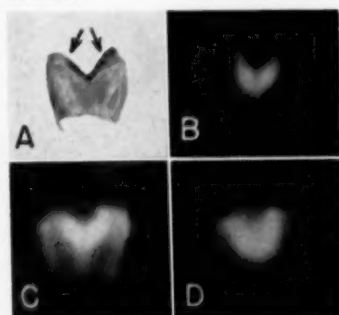
periments in cats which developed respiratory difficulties under anesthesia and which died after prolonged periods of anoxia. In these circumstances a breakdown in barrier permeability was noticed. These brains felt abnormally soft and stained with trypan blue, in spite of adequate vascular saline perfusion.

Microscopic sections showed diffuse blue coloration of the central nervous system, with grossly stained patches of extravasation of the dye around the blood vessels. Many areas of the cortex and basal ganglia revealed vital staining of their nerve cells. The lumina of the vessels contained no trypan blue. These observations proved that the vital staining was caused by increased barrier permeability and was not merely a postmortem artifact, due to insufficient perfusion.

The radioautographic picture of P^{32} deposition was interesting (Fig. 4). The areas of heavy concentration did not involve the superficial layer of the cortex and the ventricular lining alone but included the entire cortex and nuclear gray matter. In addition, the heaviest concentration of the tracer corresponded to spots which stained particularly strongly with trypan blue.

Table 2 shows the distribution of P^{32} in one of these brains as compared with a

TABLE 2.—P^{32} Content of Various Parts of the Brain *

	Cat 93 (Death from Anoxia)	Normal Control Group	
		Average	Variation
Plasma	10.0	10.0	....
Parietal cortex, Lamin I-III	9.0	4.7	3.1-7.8
Parietal cortex, Lamin III-VI	5.9	1.5	0.3-2.6
Subcortical white matter	2.9	0.4	0.0-1.2
Deep frontal white matter	2.1	0.1	0.0-0.4
Basal ganglia	3.5	0.1	0.0-0.6
Choroid plexus	18.2	34.7	20.6-44.3

* Two hours after intravenous injection of 0.1 mc. of P^{32} per Kilogram of body weight. Saline perfusion of vascular system within a few minutes before death. Values are expressed in counts per minute per milligram of tissue.

normal control. The brain of Cat 93 contains greater amounts of P^{32} than the normal average, and the difference between its superficial and its deep layers is less pronounced.

Comment

These experiments were aimed mainly to study the cerebral P^{32} concentration in bloodless brains. It was of particular interest to show whether there was any change after perfusion in the total amount and deposition pattern of the isotope in areas of greatly varying vascularity which could explain the striking difference between the phosphate uptake by the superficial layer of the cortex, on the one hand, and the basal ganglia and white matter, on the other. In addition, the effect of perfusion on extremely vascular structures of the central nervous system was evaluated. These, like the choroid plexuses and the area postrema, are composed mostly of blood vessels, and it may be conjectured that their rich deposit of isotopes in an early stage is partially due to the large amount of plasma pooled in their vessels.

It has been known from experiments using vital dyes that perfusion of the cerebral vessels with large amounts of physiological solutions does not remove the dye from those parts of the brain where it was deposited in the tissues. As a matter of fact, such a rinsing was a necessary precaution in evaluating vital staining, because the brain, if not perfused, usually showed a faint diffuse coloration caused by dye in its

Fig. 4.—Anesthesia death following cerebral anoxia, 35 minutes after injection of 0.3 mc. of P^{32}. Radioautograph of cross section of left cerebral hemisphere. Immediate post mortem vascular perfusion. Exposure time: 47 hours.
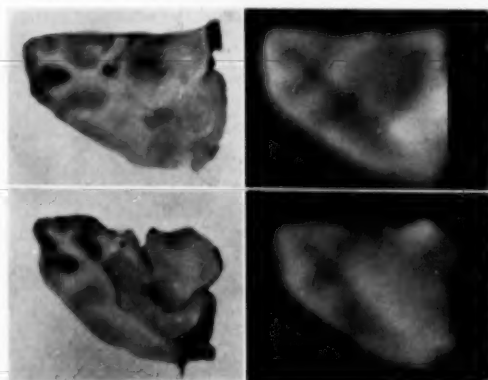
vessels. The experiments described here indicate that perfusion of short duration does not remove significant amounts of P^{32} from the central nervous system and, furthermore, that the amount of P^{32} stored in the cerebral blood vessels does not account for the concentration and pattern of deposit of the isotope in the brain even at the time of maximum plasma concentration.

Even in those experiments where perfusion followed the P^{32} administration within one hour, the most superficial layer of the cortex and the ventricular wall revealed a similar isotope concentration. This observation gives new emphasis to the concept, established in previous work, that the relationship between the relative vascularity of the nerve tissue and the rate of its phosphate uptake is by no means linear. However, there is a close relationship between the phosphate uptake of a given region and its distance from the nearest cerebrospinal fluid space.

Somewhat similar experiments were performed in rabbits by Tubiana, Gruner, Olomucki, and Sung,[14] inasmuch as they compared the cerebral isotope concentration of perfused and control animals. However, they used Br^{82}, a tracer which seems to have biological properties somewhat different from P^{32} as far as cerebral uptake is concerned. They used larger amounts of perfusate (1500 to 6000 cc.); the time of perfusion was prolonged (30 minutes to 2 hours), and during most of this time the rabbits were dead.

Nevertheless, they found that the Br^{82} content of the brain was hardly altered by perfusion. There was no reduction in the isotope concentration of the nerve tissue proper whether the tracer was injected 1 hour or 24 hours before perfusion. There was significant reduction in the Br^{82} concentration of the choroid plexuses, hypothalamus, and area postrema, mostly at the 24-hour stage. However, they clearly demonstrated that the great amount of isotope in these structures cannot be explained by their rich vascular network alone. It is of

great interest that other organs of the body (liver, muscle, etc.) lost practically their entire radioactive bromide content even after a short perfusion. They postulated that within the brain itself those regions which take up Br^{82} at the slowest rate also retain it for the longest time.

Gröntoft [10] studied the P^{32} uptake of various parts of the rabbit brain 10-80 minutes after intravenous injection of the tracer. Before killing the animals, he perfused the cerebral blood vessels with saline containing Au^{198}. This colloidal radioactive gold does not normally penetrate the wall of cerebral capillaries and was therefore used to estimate the relative vascularity of different portions of the brain. The amount of P^{32} deposited in various areas of the central nervous system was correlated with a similar standard vascularity (as determined by separate counting of the specimens for Au^{198}), but even after this correction the cerebral hemispheres, pons, and medulla were found to be more radioactive in adult rabbits than were the cerebellum and basal ganglia. Accordingly, it was shown that the unequality of the capillary population in various regions of adult rabbit brain does not explain the difference in their P^{32} uptake. In the newborn the penetration of P^{32} into various parts of the brain seemed to be closely connected with the vascularity.

My previous investigations [2] also showed that P^{32} is more uniformly distributed in fetal brains than in adults. Radioautographs of embryonic brains have not revealed the pattern of high isotope concentration in the superficial cortex, ventricular lining, and choroid plexus—so typical in adult animals brain.

Another interesting observation was made by Abood and associates,[1] who called attention to the fact that the P^{32} turnover of the corpus callosum is higher than that of the caudate nucleus, despite the greater blood flow and metabolism of the latter.

Many attempts were made in the past to correlate the relative vascularity of a certain area of the brain with its cellular structure

so as to establish relationship between blood supply and nervous function. It is generally known that the capillary population of the cortex is two to three times as great as that of the white matter and basal ganglia. Within the various layers of the cortex significant difference in the number of capillaries was described. Surprisingly enough, the internal granular layer (Lamina IV) was found to be the most vascular.[5,6,7,11] This layer of the parietal cortex numbers 35%-60% more blood vessels, according to Craigie,[6] than Lamina I or Lamina VI. Campbell[5] pointed out that Laminae I and VI of the parietal cortex have an approximately equal vascularity but different cellularity. Similar observations prompted Dunning and Wolff[7] to postulate that the greatest vascularization is related to the presence of dendrites and terminal arborizations of axons rather than to differences in the number or mass of nerve cell bodies. Nerve tissue involved in the transmission of nerve impulse from neuron to neuron is more richly supplied with blood than nerve tissue involved in conduction only within the neuron.

My data certainly reveal a discrepancy between the exchange of I^{132} of various layers of the cat's brain and their vascularity. In experiments of a few hours' duration[2] the I^{132} content of the uppermost layers (Laminae I-III) of the cat's parietal cortex was almost 10 times as great as that of Laminae V-VI, although their capillary population does not differ greatly. The significantly more abundant vascularity of Lamina IV does not manifest itself in any way so far as I^{132} uptake is concerned. The capillary population in cat's parietal cortex, expressed in millimeters per cubic millimeter of tissue, varies from 860 (Lamina I) and 870 (Lamina VI) to 1110 (Lamina IV).[5] I also found high concentration of I^{132} in the ventricular walls in tissues which, according to Campbell,[5] do not contain more than 490 to 770 mm. of capillaries per cubic millimeter.

In connection with the perfusion experiments, I performed some preliminary calculations on the amount of blood that can be expected in cerebral tissues. Campbell,[5] as well as Dunning and Wolff,[7] gave data on the regional vascularity of cat's brain, expressing it in the total length of capillaries, in millimeters per cubic millimeter of tissue. By arbitrarily assuming an average cerebral capillary diameter of 6μ, the following results emerged. On the basis of Campbell's data, the percentage of blood volume varied between 2.5% and 3.1% in various layers of the parietal cortex but was only 1.4% in the globus pallidus. The total length of capillaries in the determinations of Dunning and Wolff was about 12% less than in Campbell's; consequently, the calculated blood content amounted to 1.9%-2.5% in the parietal cortex and 1.1% in the parietal white matter.

These calculations are, naturally, not accurate. Campbell[5] and Dunning and Wolff[7] mentioned emphatically that their data are primarily of comparative value. However, White and associates,[17] using a more physiological approach in determining the relative volumes of brain, cerebrospinal fluid, and blood in the intracranial cavity, arrived at a similar conclusion. The total cerebral blood content of unanesthetized cats, measured by hemoglobin colorimetry, was about 2% of the brain volume, not including the blood stored in the large collecting veins and dural venous sinuses. This figure rose up to 4% when deep anesthesia (involving barbiturates) was applied. No distinction was made for gray and white matter, but it is certain that the relatively vascular areas of the cortex contain more than 2% of blood. The static blood volume in the rat brain was found to be 4.9% by weight of cerebral tissue.[13] According to Vladimirov,[16] brain tissue may contain from 1% to 6% of blood, depending on the method of preparation of the specimen.

These values reveal the great contrast with the vascularity of the choroid plexuses. These latter tissues contain not only more

blood vessels but also wider capillaries, 8μ-12μ, sometimes even 14μ-15μ in diameter. According to Vilstrup,[15] 75% of the weight of the normal choroid plexus in rabbits is made up by blood.

By trying to compute the amount of P³² stored in the cerebral blood vessels at any given time, one also has to take into consideration the proportional distribution of the isotope in plasma and red cells. The blood of an average cat contains 40% red cells. Two hours after intravenous injection these red cells contain less than 30% of P³², in contrast to 70%-80% of P³² in the plasma, which, again, amounts to only 60% of the capillary content. This shows why the amount of the isotope stored in the blood is not a significant factor in cerebral P³² determinations.

The situation, however, is quite different in the choroid plexus and area postrema. Here, the isotope content of pooled blood is of considerable magnitude. In the choroid plexus, the plasma content alone amounts to almost 50% of the organ's weight. The P³² content of the isolated choroid plexus, although somewhat reduced by saline perfusion, is still high enough to permit the assumption that a significant portion of the isotope is firmly incorporated in the epithelial cells. When applied to the problem of cerebrospinal fluid formation, this observation seems to be in favor of secretion rather than of pure dialysis.

Gildea and Cobb[8] proved experimentally that anoxemia of a few minutes' duration is sufficient to produce necrosis of the ganglion cells. The capillaries are certainly more resistant to anoxic damage, and even prolonged anoxia does not seem to affect the permeability of the blood-brain barrier for trypan blue in adults,[3] although this was noticed in the newborn.[9] Neither is anesthesia itself harmful to the barrier. However, Broman[3] himself stated that this does not exclude the possibility that prolonged anesthesia, which results in death, may give rise to increased permeability of the cerebral vessels. Deranged barrier permeability for

supravital trypan blue was described in fatal barbiturate poisoning.[4]

Recent experiments of Smirnov and Chetverikov[12] indicate that the rate of introduction of P³² into brain tissue increases under hypoxia. Increased passage of phosphate from plasma to brain is responsible for this phenomenon.

There was unmistakable evidence of increased barrier permeability in cats dying of anoxia resulting in deposition of trypan blue and abnormally large concentrations of P³². What made this observation even more interesting was the pattern of deposition of the vital dye, as well as of the isotope. It revealed not only that these agents were present in the brain in large amounts but also that their regional concentration followed more closely the pattern of vascularity. This seems to indicate that early and massive transcapillary exchange of P³² between plasma and brain is indeed a pathological phenomenon by itself.

Summary

Following a single intravenous injection of P³² in cats, the fastest cerebral uptake is found in the choroid plexus and area postrema. In the nerve tissue proper, the most superficial layer of the cerebral and cerebellar cortex and the lining of the ventricular system reveal the highest isotope concentration. There is no direct relationship between the rate of phosphate exchange of various portions of the brain and their relative vascularity.

A rapid saline perfusion of both carotid arteries performed from 30 minutes to 3 hours after the injection of P³² fails to change the amount and regional distribution of the isotope in the nerve tissue. The P³² content of the choroid plexus, and possibly that of the area postrema, is reduced by perfusion.

The exchange of P³² between plasma and brain increases in cats which died of anesthesia after a prolonged period of hypoxia or anoxia. Under such conditions the regional distribution of the isotope follows

more closely the pattern of the cerebral capillary network. It can be assumed that in the central nerve tissue a linear relationship between relative vascularity and rate of phosphate exchange is in itself a pathological phenomenon.

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Society Transactions

Month of Birth as Related to Psychiatric Conditions. DR. HERBERT BARRY JR.

Fourteen hundred mental hospital patients from New Jersey and Massachusetts had a seasonal distribution of birth differing markedly from that of the general population. The largest number of psychotics were born during the first four months of the year. The smallest number were born during May, June, July, and August. The difference was 21%. This finding is consistent with studies reported from the Netherlands, Switzerland, and Illinois. In sharp contrast with the distribution noted for psychotics, more births were recorded in the total population during the second trimester of the year than during the first.

A survey of the literature shows that season of birth is related to a variety of conditions. These include anencephaly, congenital cranial osteoporosis, and patent ductus arteriosus. The last of these is readily explained by its epidemiology. It is a sequel of maternal rubella in early pregnancy. Since spring is the season for German measles, women who contract rubella at that time may give birth to defective babies later in the year. Neonatal deaths, on the other hand, have a seasonal distribution of birth which resembles more closely that for schizophrenia.

Season of birth has other interesting implications. There is a difference in the average levels of intelligence of persons born at different seasons. The difference is small but consistent. This fact is well established, since it has been validated with more than 50,000 subjects. Geniuses, on the other hand, are born, paradoxically, more frequently when average IQ's are lowest. Illegitimacy and longevity also have a clear-cut seasonal birth distribution.

To attempt to explain these findings is beyond the scope of this report. Its purpose is to present evidence that seasonal differences in birth rates actually do exist and that they are especially striking in mental illness.

Discussion

DR. WILFRED BLOOMBERG: Are Dr. Barry's figures for seasonal distribution of births based on the present population, or is there any correction for age to give comparable figures at time of birth?

Moran, of the comedian team Moran and Mack, said his father kept both white horses and black horses. He had to sell the white horses because they ate too much. The only reason for this was because he owned more white horses.

Could the seasonal distribution at birth be modified by seasonal differences in mortality? Might this continue to be a factor after the 14-day period of neonatal deaths, especially in relation to respiratory infections before the days of antibiotics? The distribution shown for psychotics might be a result of some other factor that had modified the original distribution. The figures given might, therefore, represent differences in distribution of birth months of survivors. I wonder to what extent the psychotics are senile or arteriosclerotic and the distribution figures reflect some association between season of birth and longevity, rather than such a relationship with nonorganic psychoses.

DR. HUDSON HOAGLAND: Is it possible that dietary factors during pregnancy of the mother may play a role? Might not some change in a co-enzyme system occur on a seasonal basis, thus accounting for vulnerability to future psychosis, as well as for the relation noted between season of birth and longevity?

DR. WILLIAM N. HUGHES, Providence, R. I.: I am interested in the types of psychoses included. Are conditions which involve possible metabolic factors, manic-depressive psychoses, psychoses due to infections, and arteriosclerotic conditions all lumped together?

DR. ROBERT S. SCHWAB: Are there any figures for humans on differential rates of fertility from month to month? Are these differences uniform throughout the Northern Hemisphere?

DR. WILFRED BLOOMBERG: Everybody seems to be trying to look for an explanation. Can this be on some basis other than a simple casual relation between season of birth and psychosis? Are there any other questions?

DR. PAUL I. YAKOVLEV: Is there an inversion in the Southern Hemisphere?

DR. HERBERT BARRY, JR.: I am gratified that my facts were not challenged and that the discussion was centered about interpretations. Dr. Bloomberg's question, if I may paraphrase it, is whether many infants who might have become psychotics, had they survived, died instead because they were born during the summer. This might account for the smaller number of psychotics born at this season. If such be the case, these deaths must occur more than 14 days after birth, probably because of gastrointestinal disease. That is an interesting possibility. It should be explored.

In reply to Dr. Hughes, the series includes only cases in the age range from 16 to 40 years at the time of first admission. It thus excludes senile psychoses, as well as most mental illness due to toxic infections or degenerative conditions. A majority of the patients were diagnosed as schizophrenic and manic-depressive. There were also a few cases of epilepsy, mental deficiency, etc. The other investigators cited limited their cases to schizophrenia, except Peterson, who also included manic-depressives.

Since questions concerning methods of analyzing results have been raised, it should be noted that Wendell Pyle, on the basis of his data, denies that schizophrenia is related to month of birth. Yet the difference between the number of schizophrenics born in the "summer" and in the "winter" as calculated from his data is 16%. He considers this difference negligible. Actually, the difference which he describes is in the same direction as, and of comparable magnitude with, those of the other writers. His figures actually seem to confirm the findings of this study.

Dr. Hoagland's suggestion is most interesting. Dr. Sauvage Nolting compares vitamin C levels in blood at different seasons in experimental subjects with his seasonal curve for birth months of schizophrenics. He found an almost perfect inverse relationship. Prior to World War I the diet contained more vegetables from April onward. The amount of sunshine at different seasons could also affect the total amount of vitamin D available.

In reply to Dr. Schwab's question, fertility undoubtedly has seasonal variations. Most writers have held that seasonal changes in birth rate are due to factors operating at the time of conception. McArthur has commented on the increased frequency of amenorrhea during the summer months. Consequently, the striking decline in birth rates during the hottest months in such areas as Sicily and southern Spain might be on the same basis.

Dr. Yakovlev's question can be answered with an unqualified "yes," from the data which are available, all of which show an inversion in the Southern Hemisphere.

It seems clear that the season of birth no longer belongs with the occult. Further investigation may open up a new approach to some predisposing factors in mental disease.

Excretion of Epinephrine and Arterenol in Various Emotional States

I. Physiologic Aspects. DR. FRED ELMADJIAN
II. Psychiatric Aspects. DR. JUSTIN M. HOPE

Normal and psychotic subjects were studied with respect to the emotional state and excretion of epinephrine and arterenol (norepinephrine). After acid hydrolysis the urine was extracted with the aluminum oxide (alumina) adsorption method of von Euler (*Acta physiol. scandinav.* 22:161, 1951) and bioassayed by a modification of the method published by Gaddum and Lembeck (*Brit. J. Pharmacol.* 4:401, 1949). A diurnal variation was observed in the excretion of the catechol amines, with higher values occurring in the morning and the lowest during sleep. There is a greater variation in the excretion of epinephrine than of arterenol, with an average range of 1γ to 4γ in 24 hours for epinephrine and 30γ to 60γ in 24 hours for arterenol. Using excretion data obtained during infusion experiments, estimates of the secretion of epinephrine and arterenol were presented. Studies were done on (1) the players and coach of a professional hockey team, (2) neuropsychiatric patients appearing at staff conferences, (3) normal subjects in anticipatory states, and (4) psychotic subjects receiving lysergic acid diethylamide. The psychiatric data consisted of recorded longitudinal behavioral observations by trained psychiatric nurses and mental-status examinations and psychiatric rating-scale determinations by psychiatrists. Epinephrine and/or arterenol excretion was observed to be increased under these conditions. Data also included the urinary excretion of catechol amines in psychotic subjects where psychiatric rating scales were obtained during the collection period. The results indicate that, in general, the aggressive-hostile-active emotional display is related to arterenol excretion, whereas the self-effacing-fearful-passive display is related to epinephrine excretion.

Discussion

DR. CHARLES A. KANE: Dr. Elmadjian has presented us with an apparent paradox. My inquiry is based on sincere interest and is not to be taken as criticism. On rapid arithmetical calculation, from the ratio (milligram arterenol/milligrams epinephrine), if one multiplies by 15 to 20, one arrives at figures considerably below figures reported by Goldenberg and others in patients with hypertension. These patients sometimes, but not

always, manifest anxiety. How do you explain this?

Dr. WILLIAM N. HUGHES, Providence, R. I.: This is an interesting study, which may soon be applied clinically. Patients who have normal EKG's may after three or four drinks have an auricular fibrillation. The same thing may happen after stress or exercise. The fibrillation may last for a short time and reappear. Have any studies been done on arterenol and epinephrine in such patients?

Dr. HERBERT BARRY JR.: About the center player in game 2: I was interested that he had a low arterenol-epinephrine ratio to begin with, and apparently did not play so well in that game. Does the arterenol-epinephrine value before the game have a predictive value as to how an athlete will perform?

Dr. ROBERT S. SCHWAB: Is there any relation between the arterenol-epinephrine ratio and lactic acid in the blood?

Dr. DANIEL H. FUNKENSTEIN: The experimenters are to be congratulated on their fine work. These experiments are most fascinating, ingenious, and well designed.

Although the methods we used in 1949 in showing this same relationship of anger to arterenol and of anxiety and depression to epinephrine were quite different, our results were similar.

Several papers will soon appear by other investigators confirming this same relationship, and it now seems safe to state that Cannon's "fight-flight" reaction can be divided into its component emotions with different physiological accompaniments.

Again, the experimenters are to be congratulated on their ingenious experiments, which were so carefully carried out and which contribute so much to our knowledge of emotion from the psychological standpoint as related to emotion from the biochemical standpoint.

Dr. FRED ELMADJIAN: In answer to Dr. Kane's comments, there is a marked discrepancy between values obtained by fluorimetry and those obtained by bioassay techniques. The high values obtained with fluorimetry methods may be due to the possibility (1) that metabolic products of epinephrine are included in the titer in addition to epinephrine, and (2) that the reagents used in the method may have some fluorescence of their own. These as-

pects have been discussed by biochemists at several meetings. I would say that as of today I know of no really satisfactory physical method for measuring epinephrine and arterenol in biologic fluids.

The bioassay method is not recommended for routine purposes. It is a research method. In addition to the extraction procedure, there are two separate bioassay procedures to carry out for estimation of epinephrine and arterenol. It is a rather exacting and tedious process.

It should be pointed out that in humans the measurable epinephrine in urine is in all probability of adrenal origin, whereas the arterenol appears to be extra-adrenal in origin. We must be careful when comparing such urine excretion data with the data presented by Goodall for animals. The data for the latter were concerned with concentrations of epinephrine and arterenol in the adrenal medulla itself. For example, the "aggressive" lion had 50% epinephrine and 50% arterenol, while the "passive" rabbit has practically 100% epinephrine in the medulla.

Dr. JUSTIN M. HOPE: In the second game, in which the center did not play an exceptional game, his pre-game arterenol value was 0.7γ and it increased to 3.1γ during the game. In the first game, in which he played exceptionally well, his pre-game arterenol value was 3.9γ, while his post-game arterenol value was 16.1γ, which represents a greater than fourfold increase. In response to Dr. Barry's question regarding the prognostication of an athlete's performance as determined by the pre-game arterenol value: We do not have enough data to answer this question. It certainly is a very practical one. Incidentally, the coach and the players want to know the answer, also. All we can say at the present time is that from our data, in all instances, when the player's performance was exceptional, there was a sizable increase in arterenol excretion in the post-game specimen as compared with the pre-game specimen.

Dr. WILLIAM N. HUGHES, Providence, R. I.: Have there been any experiments on the excretion after alcohol?

Dr. JUSTIN M. HOPE: We have not studied alcoholics systematically. We have a few determinations on patients with delirium tremens. In these patients, in whom there was a marked expression of fear and anxiety, the epinephrine excretion was increased.

PHILADELPHIA NEUROLOGICAL SOCIETY AND NEW YORK NEUROLOGICAL SOCIETY

Ernest A. Spiegel, M.D., and George H. Hyslop, M.D., Presiding

Joint Meeting, April 6, 1956

Value of EEG Sleep Recording in Conditions Other Than Epilepsy. Dr. Daniel Silverman, Philadelphia.

This investigation determined the relative value of sleep-state EEG's in all types of patients referred for electroencephalography. Sleep-state EEG's were obtained, usually by Dormison sedation in 881 of 1000 consecutive cases. Abnormalities of significant value in the EEG interpretation were encountered in 78 cases and of contributory value in 123 cases. Sleep was most useful in the study of epilepsies; 61% of abnormalities were seen in this diagnostic category. Sleep was also of definite value in the examination of post-traumatic cases. The abnormality in almost half the abnormal records was enhanced by sleep-state dysfunctions, consisting of focal or general random or rhythmic spikes, asymmetric sharp or slow waves, or occasional spike-waves. While not crucial in brain tumors, sleep gave an indication of tumor depth. The most superficial tumors showed persistence of the slow-wave focus with suppression of sleep spindles; slightly deeper tumors showed only the persistence of the slow-wave focus; the deepest tumors, 3 cm. or more from the convexity, showed disappearance of asymmetries. The usefulness of recording during sleep in other brain diseases was less striking. Nevertheless, particularly when the waking-state record is inconclusive, sleep-state EEG's may yield valuable information and should be used whenever possible.

Discussion

Dr. Hans Strauss, New York: This is an excellent study, which has many theoretical and practical implications. Why does sleep eliminate the bilateral difference in the presence of deep lesions and accentuate it in superficial ones? Are the deep lesions such as are close to the third ventricle and cause a disturbance of the sleep mechanisms? As to patients with psychomotor seizures, it has been my experience that they tend to go asleep much more readily during the recording than other subjects. As to the psychoneurotics in whom Dr. Silverman found abnormalities, I would like to know whether the clinical picture of these patients was different from that of those psychoneurotics who showed normal records when both awake and asleep. Concerning the patients with head injuries: Were abnormalities induced by sleep only or more frequently in such patients who had epileptic phenomena? It would be very important to know exactly in which problems a sleep recording would probably help diagnostically. Sleep records are a time-consuming procedure. Therefore, from a practical viewpoint, many laboratories will not use them as a standard procedure in all cases, even less so since sleep sometimes obscures rather than brings out electroencephalographic abnormalities in some cases.

Dr. Paul F. A. Hoefer, New York: I was very much interested in Dr. Silverman's paper and in Dr. Strauss' discussion. Our own experience has been much less gratifying as far as positive findings in sleep records are concerned. We have not been able to confirm the high incidence of positive sleep records that the Gibbses have reported. I should say the over-all percentage of positive findings that are not present in the waking state is more nearly 20%, and these are mostly concentrated in two types of epilepsy: psychomotor epilepsy and epilepsy limited to sleep.

It is interesting to see that in some instances, although not in many, activation of the EEG by sleep can be found in head injuries and in brain tumors, but both these conditions are very frequently associated with seizures. I am not surprised, therefore, that there is some correlation in this.

Dr. Henry A. Riley, New York: I should like to ask Dr. Silverman whether he has found that the abnormalities present in post-traumatic states and those in functional disorders are of sufficient value to afford any real differentiation of the two etiological factors.

Dr. Daniel Silverman, Philadelphia: Rhythmic focal slow waves in sleep-state records of the eight functional cases are seen also in post-traumatic, as well as other, conditions. They are nonspecific and questionable abnormalities. In post-traumatic states we find other EEG abnormalities. The answer to Dr. Strauss' question of whether the functional cases have histories suggesting epileptic variants is "no"; true, some patients had syncopal attacks, but they showed no more abnormality than other patients without such phenomena. While it is true that more significant abnormalities are revealed in sleep with nocturnal and psychomotor epilepsy,

as Dr. Hoefer says, I do not know why his results have been so discouraging with other types of epilepsy. Significant abnormality, in my usage, appears only in sleep or is definite in sleep while merely suggestive in the rest of the record. In this series, almost 10% had significant abnormalities in sleep. This is a significant percentage of positive activation; hyperventilation, for example, is one-half, as effective. Dr. Strauss questions the advisability of sleep recording in brain tumor cases because sometimes the abnormality disappears; this disturbing phenomenon appears to indicate, from our research, valuable information—that the lesion is deep-seated. We feel that, despite the difficulty in added time involved in sleep-state recordings, the amount of useful information obtained is well worth while.

Clinicopathological Study of Tuberculous Meningitis in Adults. DR. HELENA E. RIGGS, DR. CHARLES RUPP, and DR. HOMER RAY (by invitation), Philadelphia.

Review of case records of 185 adults who died with tuberculous meningitis demonstrated that 86% had active chronic foci of the disease at the time of meningeal complication. Pulmonary activity was found in 98, but in 67 the foci were limited to extrapulmonary systems; 59 presented cerebral tuberculomata; 40% showed foci in more than one organ system. The type and distribution of tuberculosis suggests a prior hematogenous dissemination, following which organ metastases failed to regress or become reactivated. Cure of meningeal complications in adults may depend primarily upon prevention of extensive inroads of tuberculosis and control of the disease before complications develop.

Discussion

DR. MORTON NATHANSON, New York: It has become more apparent from reports of large clinics treating tuberculous meningitis throughout the world that the survival rates in adults have been decreasing with longer follow-up periods. It is a fact, too, that the survival rate is significantly lower when tuberculous meningitis coexists with miliary tuberculosis.

Among the explanations offered for the treatment failure with streptomycin, streptomycin and isoniazid, and isoniazid alone are (1) the development of resistance of the organism and (2) the increased inflammatory reaction, followed by fibrous exudates, and subsequent spinal block.

Also, it has been reported that isoniazid produces a definite increase in vascularity adjacent to the lesions, with the resultant tendency to bleeding, and perhaps further hematogenous spread.

No matter how valid these explanations may be, the inherent nature and property of the tubercle bacillus of producing chronic lesions, seemingly dormant and asymptomatic, but actually capable of harboring vital organisms, still are to be dealt with. The paper presented emphasizes this very point. The high percentage of neural and extraneural foci that were found at necropsy is significant. Many of these foci probably were undetectable clinically and may have been the source of further hematogenous dissemination.

The use of streptokinase to help penetrate these chronic lesions and the more recent use of cortisone and corticotropin early in the course of treatment to prevent the inflammatory reaction that ultimately encapsulates the organism have yet to be proved effective.

I should like to ask the authors the following questions, which could not possibly have been covered in the time allotted:

First, were there any significant differences in the histology, number, and location of lesions in the treated patients as compared with those of patients who died prior to antimicrobial therapy?

Second, were there differences in pathology in the cases not revealing extraneural foci as compared with those that did?

Lastly, were there any patients in this series who apparently were doing well on antimicrobial therapy but died suddenly of other causes, such as a coronary occlusion? If so, what was the nature of the pathology in the nervous system in such cases?

DR. HELENA E. RIGGS, Philadelphia: In answer to Dr. Nathanson, not many of our patients had been treated for the meningeal complications. The most significant histologic difference between treated and untreated cases is the alterations in the cerebral blood vessels. Treated cases show severe proliferative changes in the blood vessels adjacent to the meningeal exudate. These are very similar to the Huebner type of syphilitic endarteritis.

The pathologic process in the meninges was essentially similar in patients without demonstrable extraneural lesions and in those with numerous foci outside the nervous system.

You mentioned patients who are apparently doing well under treatment for meningitis who succumb suddenly and unexpectedly. We recently studied such a case. The patient, a college student, had an arrested case of tuberculosis of the hip and was apparently well for seven years, when he developed a mild meningitis. Under treatment, meningeal symptoms were completely relieved, when the patient suddenly had convulsive seizures and died in status. Study of the brain showed no tuberculous meningitis but revealed marked proliferative endarteritis of the vessels of the base, with extensive gliosis of the medulla as result of the arterial damage.

Cyst of Rathke's Cleft. Dr. Richard G. Berry and Dr. Nathan S. Schlezinger, Philadelphia.

Macroscopic cysts of Rathke's-cleft origin are infrequent, and those that produce clinical symptoms are exceedingly rare.

The present report concerns a case admitted to Jefferson Medical College Hospital with symptoms and signs of a pituitary adenoma. A cystic intrasellar lesion which protruded dorsally to compress the optic nerves and chiasm was decompressed at surgery, and a fragment of cyst wall was submitted for histologic examination.

The cyst wall contained strands of mucus-secreting columnar epithelium lying on a thin, fairly vascular, fibrous connective tissue stroma. Although this columnar epithelium had a pseudo-ciliated appearance in places, no definite cilia could be demonstrated. Other areas of the wall had a denser connective tissue stroma, within which were cords of pale, vesiculated cells and were reminiscent of the pars tuberalis of the hypophysis. Except for the lack of definite cilia, the lesion consisted of cells identical with those found in the remnants of Rathke's pouch within the pars intermedia of the hypophysis.

In a second case a macroscopic Rathke-cleft cyst was found in the hypophysis of a female patient with glandular symptoms that cannot definitely be attributed to pituitary hypofunction. The pituitary gland in this case was enlarged, and in the anterior lobe a cyst, measuring 7×5 mm., was found. The cyst was lined by ciliated columnar epithelium with mucus-secreting cells.

The significance of these cysts arising from Rathke's cleft is considered in the light of the development of the hypophysis and anatomical studies in the recent literature.

Discussion

Dr. Francis A. Echlin, New York: I must confess I have regarded the term cyst of Rathke's cleft as merely another name for a craniopharyngioma, a suprasellar cyst, a suprasellar epithelioma or adamantinoma, or a tumor of the hypophyseal duct or of Rathke's pouch. Certainly, in the past it has been common practice to use these terms interchangeably.

The detailed study presented here favors the view that craniopharyngiomas do arise from the hypophyseal stalk, whereas the cystic tumors under discussion arise from Rathke's cleft. At first this differentiation appears to be of purely academic interest. However, it may also be of practical value. In reviewing the literature, it has been my impression that, in contradistinction to craniopharyngiomas, all the cysts of Rathke's cleft have been small and that in none was there any calcification. The majority were situated within the sella turcica;

a smaller number were suprasellar. Generally they presented symptoms in later life, although many remained asymptomatic.

The commonest clinical syndrome produced has simulated that seen with a pituitary adenoma. In the few cases in which operation has been done, partial removal of the cyst has presumably not been followed by a recurrence, and I have had such a case. The prognosis has, therefore, seemed better than that for craniopharyngiomas arising from the stalk. If it proves true that these cysts are benign, and do not usually recur when partially removed, such information will be welcome news to the surgeon.

Dr. Abraham M. Rabiner, New York: A 5-year-old girl had appeared dull and uninterested and had cried often for five months. She vomited occasionally and for one week had complained of headache.

On admission to Mount Sinai Hospital, there was a tendency to veer to the left in walking, with slight right dysdiadochokinesia, a bilateral Babinski sign, and papilledema. Four days after admission, Dr. Charles A. Elsberg performed a suboccipital craniotomy. A large hernia persisted, and on July 1, 1927, about one month later, at the Peter Bent Brigham Hospital, Dr. Harvey Cushing reexplored the posterior fossa, found no tumor, and attempted to repair the postoperative hernia. She then received some radium and was discharged.

Two months later at home, she had a Jacksonian convulsion, with residual left-sided hemiparesis. At Peter Bent Brigham Hospital, after spinal puncture, it was concluded that internal hydrocephalus was the basis for the Jacksonian seizures.

Several weeks later, at home, she had convulsive seizures and was stuporous. She was again admitted to Mount Sinai Hospital. A ventriculogram was reported as negative. Then, because of persistent stupor and frequent convulsive seizures, Dr. Ira Cohen introduced a needle through the trephine opening in the right occipital region to a depth of 6 cm., the needle having been directed toward the right eye; a cyst was entered, from which 30 cc. of yellow fluid was aspirated. After removal of the fluid, the child regained consciousness and spoke. The needle was then reinserted more mesially, and 30 cc. of clear cerebrospinal fluid was obtained from the ventricle.

Two weeks later, the cyst was again aspirated, the fluid was replaced by air, and x-rays revealed a collection just to the right of the sella turcica. She was then transferred to Peter Bent Brigham Hospital, where Dr. Cushing operated and encountered four supratentorial cysts, three of which he was able to remove. She did well then, except that secondary sex characteristics and a severe diabetes insipidus ensued.

She was observed at Peter Bent Brigham Hospital, in all on nine occasions. She developed polydipsia, polyuria, sexual precocity, recurrent headaches, and vomiting. Her mammary glands and pubic hair were those of a 12-year-old girl. There was recurrent somnolence.

On, Dec. 27, 1929, two years later, Dr. Walter Dandy, at The Johns Hopkins Hospital, performed a craniotomy. He encountered "two tremendous suprasellar cysts." The cysts were large; the walls were thin and could not be removed. She was then admitted to the Jewish Chronic Disease Hospital in Brooklyn and for many months was comfortable and playful and walked about the wards. Severe headaches with deepening coma ensued, with death on Nov. 13, 1931.

After the paper of Drs. Alpers and Frazier appeared, I discussed this case with Drs. Cushing and Dandy. Both were of the opinion that these cysts were probably of the Rathke-cleft variety.

Dr. H. T. Wycis, Philadelphia: In view of the high operative mortality and difficulties in surgical management of Rathke-pouch tumors and related cysts, as already discussed by Drs. Echlin and Rahiner, Dr. Spiegel and I decided upon a stereotaxic approach, whereby a cystic tumor could be readily punctured and aspirated and radioactive substances (colloidal P^{32}) introduced.

The first case was that of a 13-year-old boy with convulsions, headaches, vomiting, bitemporal hemianopsia, and papilledema. Following puncture and aspiration of a cystic craniopharyngioma, there was a temporary improvement. A second puncture and aspiration, with the introduction of radioactive colloidal P^{32}, resulted in improvement, with the return of visual fields to normal except for enlarged blind spots. Improvement has been maintained for three years.

A second case, that of a middle-aged woman with headaches, papilledema, and superior altitudinal anopsia, was likewise treated. The patient is symptom-free, with a return of visual fields to normal (observation period one year).

A third case, that of a young housewife with severe headaches and amenorrhea, had an intrasellar meningioma. The lesion was treated by insertion of radon seeds through a hollow needle, which was stereotactically introduced. The needle and radon seeds could be visualized during operation by Polaroid roentgenograms. Although the patient is symptom-free, the period of observation (four weeks) is too short to evaluate this case.

Dr. Richard G. Berry, Philadelphia: I always hesitate to present a "series of one case," but I think it has been demonstrated that at least microscopically there is a difference between the Rathke-cleft cysts and the commoner craniopharyngiomas. The latter term is a little better than that of

Rathke-pouch tumor, because of the confusion in calling them both "Rathke."

In answer to Dr. Echlin, I suspect that some cases of Rathke-cleft cysts have been lost in the pathologic files under the term craniopharyngioma. The principal differential point microscopically is the cyst lining of columnar epithelium, with or without cilia, in the Rathke-cleft cysts, as compared with the adamantinomatous or squamous-cell character of the epithelial tumor known as craniopharyngioma.

In general, there seems to be a distinct difference in the morbidity rate and in the prognosis of these two types of lesions. (I speak only from the literature, for although our patient has survived very well, she has been followed for a period of less than a year.)

The Mechanism of Spasticity Following Spinal Cord Injury. Dr. Grayson P. McCouch and Dr. George M. Austin, Philadelphia.

Previously we described a potential (N$_1$a) recorded from the surface or depth of the spinal cord, attributed to afferent terminals. This potential lasts one millisecond and has characteristics of other presynaptic elements of the cord. It is more resistant to asphyxia and conditioning than are interneurons, is relatively unaffected by pentobarbital, and is completely immune to strychnine. Subsequent investigations were made on cats and monkeys, with chronic hemisection of the cord at a midthoracic level. These animals developed a somewhat spastic monoplegia in the ipsilateral hindlegs, and the cords were acutely transected at the same level at intervals of 1 to 16 weeks. At this time the amplitude of N$_1$a was recorded at the sixth lumbar dorsal-root entrance zone in response to dorsal-root stimuli, varying progressively from liminal to supramaximal. The amplitude of N$_1$a was significantly higher on the chronic side than on the acute side in response to a corresponding strength of stimulus. Similarly, the interneuronal response (N$_1$b) on the chronic side was greater in response to a given afferent strength of stimulus. Microscopic sections of the cord at the level of stimulation showed an increase of 8%-58% in the number of fibers entering the dorsal horn on the chronic side, as compared with the acute side. It is concluded from these observations that a mechanism of spasticity following spinal cord hemisection is the sprouting of new afferent terminals from dorsal roots, which tend to establish effective synaptic connections on interneuronal pools.

Discussion

Dr. Edward B. Schlesinger, New York: The clinical neurologist has to be of resilient character in this generation, in a single professional lifetime

having lived in a period which encompassed Jacksonian physiological ideas of great comfort, later the spindle and the bulbar verticular, and now the new concept of the mechanism of spasticity, presented by the authors.

I am sure the amplitudes are sufficiently different on the two sides as to be of significance, and that in the pathologic specimens justify our calling these new fibers. That leaves me very little to discuss. These old saws inevitably come to mind: Are these new fibers sufficient to form new synaptic connections? Is the experiment duplicable in man?

It is true that the spinal cord does not have the same amount of "deadness" as that which stops the fibers in the peripheral nerve from forming sufficient unions, and it is quite conceivable that such union takes place. We would all be most interested in seeing the sections.

I suggest as a clinician that it would be interesting to see subjected to this type of analysis some of the many specimens from the Army Pathology museum on spinal cords after transection.

Of course, Drs. McCouch and Austin realize that they have just embarked on a career that will require many, many years of work and study to see the effect, beginning with the cortical cells and working down, and to observe what happens where there is restoration of function.

I do not feel that I deserve any further time, but I should like again to congratulate the authors on what is to my mind a beautiful experiment, encompassing the electric, as well as the anatomical, techniques.

Dr. Louis Berlin, New York: This paper represents an interesting concept that spasticity is derived from the effects of a disturbance at the level of lesion. Apparently the authors have referred to this as a mechanism of spasticity, and I assume that they therefore take cognizance of the fact that the phenomenon of spasticity is the result of a disturbance in which more than one factor plays a role.

It is evident that the regulatory function of the central nervous system, as, for example, in its regulation of muscle tone and posture, is dependent not on a single factor but upon the interaction of many elements. Investigation, therefore, generally is directed toward evaluation of the relative roles of these elements, and, furthermore, the relative roles of these individual factors having been studied, toward determination of the circumstances under which each factor operates optimally, maximally, and minimally.

The first question, therefore, is under what circumstances of stimulation are these fibers most effective in so altering the muscle reactivity as to intensify spasticity. Are they functionally more effective in influencing reactivity than are the more caudal, uninjured afferent fibers?

It was found a long time ago that in spinal dog a single shock of Sherrington's "electrical flea" evoked a scratch reflex, but repetitive stimulation was followed by inactivity. Our own observation on spinal man has confirmed this, that prolonged faradization of the skin resulted in a state of spinal inhibition, and this was observed also by Jefferson and Schlapp, who found that prolonged and repetitive stimulation of one dorsal root resulted in a widespread depression of recordings from the ventral roots.

It is axiomatic that the effect of a stimulus is dependent upon the existing central excitatory or inhibitory state. It then becomes a question as to what are the effects of the resting, tonic, or constant influence of these N-1 fibers, and how these impulses are influenced by other fibers acting simultaneously or in close association temporally with them.

Another view of the effect of the spinal cord section may perhaps be derived from the principles relating to the effects of damage to any part of the central nervous system. Under these circumstances reactivity still occurs, but there is a decrease of the reactive reserve. Activity persists, but the repertoire of function is reduced and there is a progressively narrower range of adaptive capacity. Spasticity, therefore, is associated with such a rigidity or limitation in the range of adaptive responsiveness.

The authors have made interesting observations on the local changes at the site of cord lesion. Essentially, the problem is this: Do the fibers they describe contribute significantly to spasticity, or is it the factors operating under the conditions of isolation from suprasegmental innervation that play the preponderant role?

Chronic Depth Recording in Focal and Generalized Epilepsy, an Evaluation of the Technique. Dr. A. Earl Walker and Dr. Michael Ribstein, Baltimore.

In six patients suspected of suffering from epilepsy, depth electrodes composed of braided insulated copper wire were inserted by a freehand technique into subcortical structures. The localization of these electrodes was confirmed by roentgenograms of the skull after pneumoencephalography. Three exposed tips were present on each set of electrodes, and customarily the electrodes were inserted into the following regions: both medial frontal regions; both anterior temporal regions, the tips presumably entering the nucleus amygdala; both basal ganglia, and one or both thalami. The insertion of the needles was carried out with the use of local anesthesia, or in some cases of general anesthesia, and recording made daily for a period of from 3 to 15 days in various

physiological states, with or without pentylenetetrazol U. S. P. (Metrazol) activation or electrical stimulation of the depth electrodes. The electrical excitation was carried out with a sine-wave current, using 2-5 volts at 60 cps for five seconds. In three cases there was spontaneous isolated spiking, as well as spontaneous seizures, apparently beginning in subcortical structures, sometimes from the same focus and at other times from various foci. In three cases no spontaneous seizures were observed in cortical or subcortical electrodes, but in all cases after-discharge was obtainable with the parameters of stimulation used. At times these after-discharges were associated with clinical manifestations similar to those observed in the spontaneous attacks of the patient.

The value of chronic depth recording is indicated by the fact that multiple foci could be demonstrated in subcortical structures, that at times activity could be demonstrated in subcortical nuclei when scalp leads showed no evidence of such activity, and, finally, that it was possible to produce by electrical stimulation the aura or attack which some patients experienced in their usual spontaneous seizures.

Discussion

DR. PAUL F. A. HOEFER, New York: Depth recording in psychotic and epileptic patients has led to a wealth of information in Dr. Walker's laboratory, as well as in that of Dr. Spiegel and in other research centers.

By this method we have learned a great deal about basic activities originating in subcortical centers and in the white matter. These activities are not necessarily reflected in the recordings from the intact head or in cortical tracings obtained at operation. Depth recording in combination with stimulation through the same electrodes has enabled these investigators to elucidate some of the problems of origin and spread of focal and generalized seizures.

I would like to ask two questions: 1. Were Drs. Ribstein and Walker able to reproduce psychomotor attacks by stimulating the amygdala? In the hands of other investigators only generalized convulsions have been produced. 2. Have they found new evidence of spread of seizure activity in the corpus callosum and other commissures?

DR. H. T. WYCIS, Philadelphia: With Dr. Spiegel, we were interested in recording from the pallidum, as well as the thalamus, and sometimes also the caudate nucleus, in cases of generalized epileptiform convulsions refractory to the usual medications, particularly in view of Hayashi's finding of extrapyramidal conduction of corticofugal impulses, and partly because pallidal impulses reach the nucleus ventralis anterior and may act upon the diffuse thalamic projection system. In four cases there were findings of pallidal seizure discharges, which encouraged us to try a pallido-ansotomy. One patient had Jacksonian attacks caused by brain abscess. The observation period is too short to permit us to draw definite conclusions. The second patient had tonic-clonic seizures and showed definite pallidal discharges with hardly noticeable EEG abnormalities. Pallidotomy did not significantly influence the seizures, probably in part because of the patient's alcoholism. The third patient had prior to operation an average of eight seizures a month despite heavy medication. After pallidotomy he had only one seizure during six months. The fourth patient, observed with Dr. Baird, was a child with tuberosclerosis, showing a calcified nodule in the caudate nucleus and seizure discharges, mainly in the pallidum. The patient had 250 petit mal attacks daily and 2 to 3 grand mal seizures weekly. During one year following placement of a lesion in the region of the nodule and the ansa lenticularis there have been no attacks despite drastic reduction of the medication.

Abstracts from Current Literature

Anatomy and Embryology

PERINEURONAL SATELLITE CELLS IN THE MOTOR CORTEX OF AGING BRAINS. R. H. BROWNSON, J. Neuropath. & Exper. Neurol. 15:190 (April) 1956.

An increase in the number of perineuronal satellite cells is a phenomenon that has long been associated with an abnormality in the nervous tissue, but many observers have noted that such an increase does not necessarily indicate necrobiosis in neurons. In a previous report Brownson noted that perineuronal satellitosis was present not only in aged human brains but also in very young normal brains. Upon this basis, the author studied 24 brains of patients who had been normal neurologically and noted the number of perineuronal satellite cells based upon a count of 100 cells per specimen. The ages ranged from 3.5 to 89 years. He found an average of 51% oligodendrocytes, 40% astrocytes, and 9% microgliocytes. There were no marked changes in the ratios of oligodendrocytes, astrocytes, and microgliocytes in the ages of 3.5 to 89 years. The proliferation of perineuronal satellite cells results from an increase in neurological tissues with an increase in all cell types. There was evidence of oligodendroglia neuronophagia of nerve cells in a few cases beyond the fifth decade.

MANDEL, Philadelphia.

Physiology and Biochemistry

CEREBRAL VASCULAR INSUFFICIENCY—AN EXPLANATION OF THE TRANSIENT STROKE. E. CORDAY, S. ROTHENBERG, and S. M. WEINER, A. M. A. Arch. Int. Med. 98:683 (Dec.) 1956.

The authors present three cases in which transient attacks of focal neurologic impairment developed against a background of sudden systemic hypotension, in two instances due to cardiovascular disease (hyperactive carotid sinus and ventricular tachycardia), and in the third, to shock (gastric hemorrhage). It is hypothesized that a sudden fall in systemic blood pressure to a critical level may produce focal cerebral ischemia especially involving areas in which a reduction of the diameter of vessels is present, such as would result from atherosclerosis. This is particularly likely in the event of inadequate collateral circulation, and it is additionally stressed that such effects are prone to occur in end-artery systems, such as the cerebral and coronary, in the latter of which the term "acute coronary insufficiency" has been used to describe the analogous condition. The authors experimentally confirmed the above assumptions by producing in monkeys with ipsilateral partial carotid obstruction focal electroencephalographic alterations upon reducing the blood pressure and then abolishing these alterations by restoring the normotensive state (by either transfusion or pressor drugs). It is considered likely that many examples of focal and recurring cerebral disorders (hemiparesis, aphasia, hemianopsia, Jacksonian seizures) are to be regarded as manifestations of localized cerebrovascular insufficiency, especially when sudden systemic hypotension occurs with severe cerebral arterial disease. The treatment for this condition, as well as the more generalized cerebral vascular insufficiency manifested by coma or generalized epileptic seizures (in which there is usually little cerebrovascular disease), is the restoration of normal blood pressure levels.

PARSONS, Montrose, N. Y.

REVERSIBLE POSTOPERATIVE NEUROLOGICAL SYMPTOMS. L. G. BARTHOLOMEW and D. A. SCHOLZ, J. A. M. A. 162:22 (Sept. 1) 1956.

Bartholomew and Scholz report five cases in which overt neurological signs and symptoms associated with water intoxication and an unrecognized depletion of sodium developed during the immediate postoperative period. The diagnosis was verified by studies of the blood electrolytes and by the prompt clinical response to the intravenous administration of sodium chloride.

Four of the five patients were women. All the patients were in the older age group, a finding which agrees with the usual age incidence noted in previous reports on water intoxica-

tion. Definite predisposing factors for deficiency of sodium chloride were present in three of the five patients, namely, prolonged preoperative periods of deprivation of salt, in two patients, and excessive loss of electrolytes from the gastrointestinal tract, in one patient.

Th possibility of water intoxication and concomitant depletion of sodium should be considered in all cases in which hemiplegia, convulsions, or coma develops during the postoperative period. Water intoxication can be prevented by careful consideration and supervision of the postoperative administration of fluids.

ALPERS, Philadelphia.

PAROXYSMAL DYSPHASIA AND THE PROBLEM OF CEREBRAL DOMINANCE. H. HÉCAEN and MALCOLM PIERCY, J. Neurol. Neurosurg. & Psychiat. 19:194 (Aug.) 1956.

Hécaen and Piercy report their results in the analysis of the incidence of paroxysmal dysphasia in association with epileptic auras and equivalents with reference to the side of a unilateral focus of the cerebral disturbance and to handedness. They noted that paroxysmal expressive dysphasia occurred more frequently in left-handed patients with aura than in right-handed patients with aura irrespective of the side of the epileptic focus. In right-handed patients, the incidence of expressive aphasia was greater in left-sided disturbance than with right-sided disturbance. There was no such difference in the left-handed patients. Receptive aphasias were rarely encountered except in right-handed patients with left-sided cerebral foci, and the incidence was about one-half of the expressive aphasia group.

The authors believe that the differences in the aphasia seen in right- and that seen in left-handed patients in association with unilateral lesions or foci are consistent with the differences between the two groups in the degree of cerebral specialization for language with regard both to bilateral representation and to representation within a single hemisphere.

MANDEL, Philadelphia.

ELECTROPHORESIS OF SERA IN MULTIPLE SCLEROSIS AND OTHER NEUROLOGICAL DISEASES. E. M. PRESS, J. Neurol. Neurosurg. & Psychiat. 19:222 (Aug.) 1956.

In a large percentage of cases the cerebrospinal fluid γ-globulin is increased in multiple sclerosis but the serum γ-globulin is not raised. In this study, Press compared the serum proteins of 11 normal patients, 28 patients with multiple sclerosis, and 9 patients with other organic disease of the nervous system.

The disease was active in 22 of the multiple sclerosis patients in this series, but only 12 had increased a_2-globulin concentration. Of six patients in whom the disease was inactive, four had increased a_2-globulin concentration. She concluded that there was no correlation of the a_2-globulin concentration and the activity or duration of the disease, the age of the patient, or the colloidal gold reaction of the spinal fluid. The a_2-globulin was also found to be elevated in the nine other neurological diseases, as well as in fevers, malignant disease, and collagen diseases, hence the increase in a_2-globulin was not specific.

MANDEL, Philadelphia.

HYPOTHERMIA AND CEREBRAL VASCULAR LESIONS. H. I. ROSOMOFF, J. Neurosurg. 13:244 (July) 1956.

Rosomoff interrupted the middle cerebral artery of the dog at normal body temperature and during hypothermia at 22-24 C (71.6-75.2 F). When the artery was occluded at normothermic temperatures, the animal developed a contralateral hemiparesis and ipsilateral forced circling movements, secondary to a cerebral infarct. When interruption of the artery occurred at hypothermic temperatures, either no infarct developed or small lesions in silent areas of the brain were found.

Rosomoff concluded that hypothermia produces a reduction in cerebral blood which facilitates hemostasis. In addition, hypothermia produced a decrease in cerebral blood volume, enhancing surgical exposure and a diminution of intracranial pressure. Thus, hypothermia may be of value in the surgery of vascular lesions, as well as a tool in the study of cerebral function in health and disease.

MANDEL, Philadelphia.

Neuropathology

THE PATHOLOGICAL EFFECTS OF CEREBRAL ARTERIOGRAPHY. T. CRAWFORD, J. Neurol. Neurosurg. & Psychiat. 19:217 (Aug.) 1956.

Lesions resulting from arterial puncture were studied in necropsy material from 75 patients dying at intervals varying from a few hours up to eight months after cerebral arteriography.

In this series reported by Crawford, the most important complication was occlusive thrombosis of the punctured vessel. Mural thrombosis at the site of arterial puncture was a frequent finding of minor degree in many cases. This consisted of lateral extensions of the fibrin plug in the needle track over the adjacent parts of the intima. A thrombus of this kind usually resulted in localized thickening of the intima, but if it became pedunculated or polypoid, the thrombus predisposed to cerebral embolism, which was a second important complication of arteriography. In five cases multiple cerebral infarcts secondary to mural thrombi in the internal cartoid artery were found. Concealed hemorrhage, consisting of blood spreading within the carotid sheath or rupturing through the sheath into the neck and mediastinum, was also encountered in this series. Hemorrhage was minimal in young subjects and was most marked in elderly hypertensive patients or when the vessel was repeatedly punctured.

Two examples of a small false aneurysm found at the site of the needle tract were encountered. Microscopic examination revealed the false aneurysm to be outside the media, but communicating with the lumen by an endothelized tract. Small dissecting aneurysms, consisting of blood-filled cavities, were found in nine instances.

Crawford states that in this series no attempt was made to determine the frequency of each of the pathological lesions noted, since many specimens were submitted because of their unusual occurrence. Advanced age, hypertension, and atherosclerosis were found to be three associated factors in a large number of thrombosis cases.

MANDEL, Philadelphia.

REGENERATION AND DEVELOPMENT OF SENSORY NEURONS IN VITRO. E. R. PETERSON and M. R. MURRAY, J. Neuropath. & Exper. Neurol. 15:288 (July) 1956.

Peterson and Murray studied appropriately cultured isolated embryonic chick ganglia (4-15 days *in ovo*) and describe the progressive maturation of the interrelated elements composing the ganglia in the living state.

In the first week of growth in vitro the axons elongate and thicken. During the next several weeks the greatest changes are observed in the nerve and Schwann cells and in the supportive elements. The stages of development of the Nissl substance to a mature pattern are described and are similar to that of embryonic development.

Concomitant with the development of the soma, the axon thickens and is enveloped by Schwann cells. A fibrous material forms a capsule around the cell and its complement of Schwann cells. Before the Nissl pattern is fully mature, myelin begins to appear in isolated segments, with a Schwann cell often at the center of such a segment. It is suggested that small lipid granules in Schwann cells may play a role in the elaboration of the myelin. The extent of myelination is greatly influenced by the embryonic tissues also present: Cartilage and epithelium are highly favorable; spinal cord, antagonistic.

The authors believe both axons and Schwann cells are necessary for production of myelin. Certain characteristics of axons favor the adherence of the Schwann cells, and since the myelin develops in separate segments, the stimulation of myelin production, or actual production, must depend on the Schwann cell.

SIEKERT, Rochester, Minn.

A COMPARATIVE STUDY OF EXPERIMENTAL ALLERGIC NEURITIS IN THE RABBIT, GUINEA PIG, AND MOUSE. B. H. WAKSMAN and R. D. ADAMS, J. Neuropath. & Exper. Neurol. 15: 293 (July) 1956.

Waksman and Adams injected homologous or heterologous central and peripheral nervous tissue plus the Freund adjuvants into several species of laboratory animals. Rabbits and mice injected with peripheral nervous tissue plus adjuvants developed lesions only in the peripheral nervous system. When injected with central nervous tissue and adjuvants, these animals developed central and peripheral lesions, the latter in about three-quarters of the animals. The guinea pig developed lesions in both areas of the nervous system after injection with either type of antigen. However, among the guinea pigs receiving central nervous tissue antigen, about half developed disease limited to the central nervous system, and none had peripheral lesions alone. Among those which received peripheral nervous tissue antigen, the reverse was the case.

The findings are interpreted as indicating that the antigens present in the myelin of the peripheral and central nervous systems differ, but that immunological cross reactions occur between the two.

The lesions observed in the central nervous system were those of experimental allergic encephalomyelitis. In the peripheral nervous system the lesions consisted of focal perivascular collections of histiocytes and some lymphocytes. These cell infiltrates were found in areas of myelin breakdown, with a relative sparing of axis cylinders. The name "experimental allergic neuritis" was given to this disease.

SIEKERT, Rochester, Minn.

NEUROPATHOLOGICAL CHANGES IN HEREDITARY NEUROPATHIES: MANIFESTATION OF THE SYNDROME HEREDOPATHIA ATACTICA POLYNEURITIFORMIS IN THE PRESENCE OF INTERSTITIAL HYPERTROPHIC POLYNEUROPATHY. J. CAMMERMEYER, J. Neuropath. & Exper. Neurol. 15:340 (July) 1956.

Cammermeyer restudied the neuropathological material in several cases with Refsum's syndrome, which consists of (a) polyneuritis with paresthesias, ataxia, and muscular atrophy; (b) retinitis pigmentosa; (c) papillary abnormalities; (d) hearing difficulties, and (e) miscellaneous changes, including electrocardiographic and bone abnormalities. The principal manifestation of the illness was interstitial hypertrophic polyneuropathy (Dejerine-Sotta) with neural muscular atrophy, retrograde atrophy of the anterior horn cells, secondary atrophy of the fasciculus gracilis, and deposition of fat in the affected nerves. Some demyelination in the brain stem tracts, particularly the medial lemniscus, and diffuse loss of cells in the inferior olive were observed. The cerebral hemispheres contained fat-filled neurons in some instances and fat droplets lying free in others.

It would appear that the syndrome of Refsum belongs to the group of hereditary nervous maladies that affect peripheral nerves, muscles, and the central nervous system. The theories of pathogenesis are discussed. Cammermeyer offers the tentative explanation that an inherited anomaly influenced the biochemical or physical properties of myelin, so that disruption between the protein and lipid layers occurs, a process he terms delamination.

SIEKERT, Rochester, Minn.

Meninges and Blood Vessels

CRYPTIC ARTERIOVENOUS AND VENOUS HAMARTOMAS OF THE BRAIN. J. V. CRAWFORD and D. S. RUSSELL, J. Neurol. Neurosurg. & Psychiat. 19:1, 1956.

Crawford and Russell report 20 cases of spontaneous cerebral and cerebellar hemorrhage in the younger age group, all the patients being less than 40 years of age; 15 were less than 20 years of age. In each instance the hemorrhage was due to a vascular anomaly, which because of its size or location was difficult to locate. For this reason Crawford and Russell propose the use of the term "cryptic hamartoma." The cases were divided into three groups according to the anatomical location of the lesion: Group I, related to the cerebral convexities; Group II, central cerebral; and Group III, cerebellar.

In the first group, of 10 cases, there were 6 fatalities, and in all but 2 cases the lesion was in the area of supply of the middle cerebral artery, and 1 each was in the distribution of the anterior or posterior cerebral artery. On inspection, the lesion was usually found upon the surface as a small cluster of tortuous vessels related to the underlying anomaly, but occasionally it was buried in a sulcus and the surface vessels appeared normal. The size varied, and microscopic examination revealed the vascular anomalies to be composed of enlarged and tortuous veins and arteries occupying a restricted area of the pia and brain adjacent to the hemorrhage. The intima and media were abnormal, with the muscle and elastic coats showing either hypoplasia or hyperplasia. Varying amounts of fibrous gliosis with foci of macrophages containing hemosiderin were noted.

The patients in Group I were well until the time of collapse, when they complained of headache and vomiting, followed by loss of consciousness. Intraventricular hemorrhage was present in some cases, and this was followed by death.

In Group II, the lesions were predominantly venous, involving the tributaries of one of the lesser veins of Galen. In this series, of four cases, the onset was also dramatic; all patients died.

In Group III, there were six cases, in three of which the patients died and in three were relieved by surgery. Three patients had signs of increased intracranial pressure with cerebellar signs, and these lesions had to be differentiated from cerebellar tumors.

MANDEL, Philadelphia.

Diseases of the Brain

NEUROLOGICAL AND PSYCHIATRIC SIGNS ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS. E. C. CLARK and A. A. BAILEY. J. A. M. A. 160:455 (Feb. 11) 1956.

Patients with systemic lupus erythematosus may suffer involvement of any part of the nervous system. It is a disseminated disease accompanied by severe manifestations of neurological and psychiatric dysfunction. This association is shown by Clark and Bailey's analysis of 100 clinically diagnosed cases, in 28 of which signs or symptoms of neuropsychiatric disease occurred.

From a neurological standpoint, generalized and focal convulsions, hemiplegia, double vision, choked disks, polyneuritis, subarachnoid hemorrhage, nystagmus, vertigo, choreiform movements, monoplegia, paraplegia, quadriplegia, aphasia, intention tremor, neuropathy of the facial nerve (Bell's palsy), cortical blindness, and the decerebrate state were noted. Psychiatric findings associated with the disease were symptoms of anxiety associated with fear of impending disaster, personality changes, and memory defects. Other manifestations were emotional lability, mental deterioration, depression, hallucinations occurring with fever, and paranoid and obsessive reactions. The onset of these difficulties was usually not associated with cortisone or corticotropin therapy, uremia, hypertension, or the last week of the patient's life. The explanation probably lies in vascular changes in the blood vessels of the nerve structures.

ALPERS, Philadelphia.

SYMMETRICAL CEREBRAL CALCIFICATION ASSOCIATED WITH PARATHYROID ADENOMA. W. P. KNUTH and P. KISNER. J. A. M. A. 162:462 (Sept. 29) 1956.

Knuth and Kisner report a case which very closely resembles the sequence of events reported as occurring in hypoparathyroidism, associated with bilateral cerebral calcification. The onset of the disease is early in life and is characterized by intermittent episodes of convulsive seizures and gradually progressive intellectual and emotional deterioration.

When the patient, a man of 58, was first seen in hospital, about three years before his death, blood chemistry determinations indicated a relative hyperparathyroidism rather than a parathyroid deficiency. At autopsy a large cystic adenoma was found in a parathyroid gland and microscopic calcific deposits were present in the kidneys.

The cause of parathyroid adenomas is unknown. In this case one can only speculate as to the relationship of the bilateral cerebral calcification, the parathyroid adenoma, and the hyperparathyroidism, as noted by blood chemistry determinations. It might be assumed that a state of hypoparathyroidism may have existed for many years and that the parathyroid adenoma developed as a process of compensatory hyperplasia until eventually a state of hyperparathyroidism was attained.

No conclusions are drawn from this case. It is presented primarily from the standpoint of its unique clinical and postmortem findings.

ALPERS, Philadelphia.

MENINGOENCEPHALITIS IN INFECTIOUS MONONUCLEOSIS. E. P. FRENKEL, C. B. SHIVERS JR., P. BERG, and T. N. CARIS. J. A. M. A. 162:885 (Oct. 27) 1956.

The authors report a case of infectious mononucleosis with associated meningoencephalitis in which recovery occurred rapidly after the administration of cortisone. The patient, a 19-year-old youth, presented a picture of infectious mononucleosis and was started on therapy consisting of diet, vitamin supplements, bed rest, and general supportive care. Since he continued to have fever and showed progressive systemic symptoms, cortisone therapy was instituted on the seventh hospital day. The patient responded very well and was convalescing without incident except for an episode of epistaxis on the 17th hospital day. The dosage of cortisone was slowly tapered and therapy discontinued after seven days. On the 19th hospital day the patient again became febrile, and nuchal rigidity subsequently developed. The entire neurological examination was within normal limits. Blood for cultures was drawn, and after 12 hours a Gram-positive coccus appeared to be growing on one of them. The cerebrospinal fluid was negative on smears and cultures. Although an infectious mononucleosis type of meningoencephalitis was suspected, the one early presumptive positive blood culture led to the treatment of the patient with large doses of sulfadiazine and penicillin. Antimicrobiotic therapy was continued for seven days, without any real abatement in fever, symptoms, or clinical signs. During this period neurological deterioration of the patient was noted.

On the 26th hospital day therapy with both penicillin and sulfadiazine was discontinued and the patient was started on therapy with cortisone, 300 mg. per day. The patient responded very dramatically to cortisone therapy, with lysis of his fever in 36 hours. Within 72 hours almost all neurological signs completely cleared. The patient convalesced without further event.

Central nervous system involvement in infectious mononucleosis occurs in approximately 1% of all cases of the disease. In the majority of cases with clinical neurological involvement, the symptoms become manifest in the first to the third week of the illness. Generally, the course of infectious mononucleosis is a self-limited one, and the disease is relatively benign. The appearance of neurological manifestations adds a grave note to the prognosis. In the 71 collected cases of neurological involvement recorded from the literature by Leibowitz, there was a mortality rate of 11%.

This patient's rapid and dramatic improvement after the institution of steroids in the therapy suggests that cortisone may be of value in the meningoencephalitis of infectious mononucleosis.

ALPERS, Philadelphia.

A CLINICAL CORRELATION BETWEEN ENCEPHALOPATHY AND PAPILLEDEMA IN ADDISON'S DISEASE. A. JEFFERSON, J. Neurol. Neurosurg. & Psychiat. 19:21 (Feb.) 1956.

Jefferson reports two cases of Addison's disease with papilledema. In one case the adrenal failure was secondary to a chromophobe adenoma of the pituitary gland; in the second case there occurred the picture of cerebral edema with Addison's disease of idiopathic origin. Jefferson believes that the adrenal insufficiency was directly related to the papilledema and that some metabolic abnormality was responsible for this finding.

MANDEL, Philadelphia.

THE AMNESTIC SYNDROME. V. A. KRAL, Monatsschr. Psychiat. u. Neurol. 132:65 (Aug.-Sept.) 1956.

Kral analyzed the two most significant features of Korsakoff's psychosis, namely, impaired immediate recall and loss of recent memory as a consequence of failure of integration of affective perceptual components of a given situation with similar previous experiences having a meaningful personal impact. This integrative difficulty comprises the third and most chronic phase of a nonspecific reaction to diffuse brain damage, the first two being coma and delirium, and has been termed the amnestic syndrome. In a survey of pathological findings noted in a wide variety of cases with the amnestic syndrome, the author cites the frequency of lesions in the region of the periventricular gray matter, especially in the mammillary bodies, and also in the limbic areas implicated by Papez in his "harmonious" mechanism. It is suggested that the brain stem and diencephalic lesions are so placed as to impinge upon Magoun's reticular activating centers, with impairment of conscious awareness, and that the limbic lesions may result in further alterations in attitude or affective set toward otherwise personally meaningful situations. The unusual frequency of lesions of the mammillary body, which has rich connections both with brain stem structures and with the hippocampus, anterior nucleus of the thalamus, and cingulate gyrus, is stressed in this connection.

PARSONS, Montrose, N. Y.

Diseases of the Spinal Cord

LOWER EXTREMITY PAIN SIMULATING SCIATICA. M. SCOTT, J. A. M. A. 160:528 (Feb. 18) 1956.

An intramedullary or extramedullary tumor of the cervical and high thoracic spinal cord is an infrequent cause of burning or sharp pain referred to a lower extremity. Six cases in which the explanation was found in lesions of the thoracic and cervical parts of the spinal cord are presented to illustrate this fact. The patients were all women past 50 years of age. In one case 16 years had elapsed between first symptoms and ultimate diagnosis; in another, 5½ years of severe symptoms and varied disabilities were accompanied by so much anxiety that examination became difficult. The pain may be confused with that caused by herniated intervertebral disk or by an intraspinal or extraspinal lesion involving the roots of the cauda equina or the peripheral portion of the sciatic nerve.

The investigation of persistent lower-extremity pain not due to extraspinal cause is incomplete without an iophendylate (Pantopaque) myelogram. Since pain in a lower extremity is frequently due to a herniated intervertebral disk in the low lumbar canal, the tendency has been in such cases to limit the myelography to the lumbar area. If the fluoroscopic phase of the lumbar myelogram is negative or equivocal, the contrast medium should be run through the entire thoracic canal and, if need be, through the entire cervical canal to rule out a tumor in these areas. The cases here collected are unusual in that they were explained by the finding of benign, slow-growing tumors so high up in the spinal cord.

ALPERS, Philadelphia.

MENINGEAL DIVERTICULA OF SACRAL NERVE ROOTS (PERINEURIAL CYSTS). K. J. STRULLY, J. A. M. A. 161:1147 (July 21) 1956.

Strully reports four cases of meningeal cysts in the sacral region, supplementing a series previously reported. Low back pain, unexplained by usual diagnostic procedures and resistant to ordinary treatment, led to the use of delayed myelography with iophendylate, which showed the existence of diverticula of the root sheaths of various sacral nerves.

The x-ray evidence was confirmed at operation. Laminectomy revealed not only the cysts filled with contrast medium but also extensive cavitations in the bone. Opening the cysts and resecting the affected nerve roots was followed by great improvement in the patient's condition in each case.

These cases show that cyst-like diverticula of the nerve sheaths may develop in adult life, that they may cause local pressure atrophy in bone, and that they are amenable to treatment.

ALPERS, Philadelphia.

CERVICAL SPONDYLOSIS AND COMPRESSION OF THE SPINAL CORD. J. BRAHAM and E. E. HERZBERGER, J. A. M. A. 161:1560 (Aug. 18) 1956.

Spondylosis of the cervical vertebrae may give rise to a syndrome of cord compression with a variety of subjective and objective neurological disturbances in the upper and lower limbs. Indentation of the cervical part of the spinal canal by protrusion of intervertebral disks and by osteophytic lipping produces these symptoms directly by mechanical injury and indirectly by effects on the movement of blood and cerebrospinal fluid. Repeated minor traumas of the cord during flexion-extension movements of the neck are believed to be a causative factor.

In cases of cervical cord lesions due to spondylosis, an attitude of critical alertness in differential diagnosis is important, as shown by two cases here reported. In one case, the extensive paralyses in the patient were found to result from amyotrophic lateral sclerosis, in addition to osteophytes that had caused marked narrowing of the disk space at the fourth and fifth cervical levels. In the second case, gross spondylotic changes in the cervical region coexisted with a sarcoma that was blocking the canal completely in the thoracic region. Diagnosis depends on cerebrospinal fluid manometry and myelography, which is indispensable in the avoidance of errors.

Laminectomy, with section of the dentate ligament, was done in six cases of chronic cord compression by cervical spondylosis. No improvement resulted in one case, and in two the results were hard to assess. But in three there was partial success; and two of these patients were relieved of symptoms and enabled to return to their occupations. This experience suggested that surgical treatment be reserved for the patient with a short history and a downhill course; surgical treatment does not seem advisable in the management of the patient with advanced paralysis.

ALPERS, Philadelphia.

Peripheral and Cranial Nerves

A FAMILY WITH THE PROGRESSIVE HYPERTROPHIC POLYNEURITIS OF DEJERINE AND SOTTAS. P. D. BEDFORD and F. E. JAMES, J. Neurol. Neurosurg. & Psychiat. 19:46 (Feb.) 1956.

Bedford and James report a family of five generations in which progressive hypertrophic polyneuritis was inherited as a heterozygous dominant characteristic. Eight members were affected with varying degrees of severity. The cases revealed muscular weakness and atrophy with sensory changes. Thickening or enlargement of the peripheral nerves was also present. Microscopic examination demonstrated pathognomonic changes, consisting of the

onion arrangement of a hypertrophic neuritis. Degeneration was present, with an increase in the number of Schwann nuclei, as well as an increase in collagen around some of the fibers. The histologic diagnosis was made in only one case.

MANDEL, Philadelphia.

NEUROPATHIES DUE TO VITAMIN DEFICIENCY. H. M. ZIMMERMAN, J. Neuropath. & Exper. Neurol. 15:335 (July) 1956.

Microscopic study of thiamine-deficient animals reveals, in the early stages, demyelination of the peripheral nerves. The fat lies at first wholly within the medullary sheaths, and later it is found in the intermedullary connective tissue. At a variable interval after the beginning of demyelination, evidence of axis-cylinder destruction appears, with ballooning and fragmentation. An actual inflammatory cellular reaction is never observed.

In chronically deficient animals with peripheral neuropathy, demyelination of the spinal cord is seen, characteristically of the posterior columns.

SIEKERT, Rochester, Minn.

News and Comment

American Board of Psychiatry and Neurology, Inc.—The American Board of Psychiatry and Neurology, Inc., announces the following schedule of examinations:

New York . . . Dec. 16 and 17, 1957
San Francisco . . . March 17 and 18, 1958

Changes in Examination Procedures in Basic Neurology for Neurologists Only. The Board has changed the organization and procedure of the examinations in Basic Neurology. Candidates may have been told of the type of examinations in Basic Neurology previously utilized by the examining sections. This consisted of two duplicate one-hour examinations in Basic Neurology. It is not the wish of the Board to surprise candidates by unannounced changes in the examination procedure.

Candidates will have two one-hour examinations in Basic Neurology.

1. One one-hour examination in (a) gross pathology, (b) microscopic pathology, (c) neuroanatomy.

2. A second one-hour examination in (a) neuroroentgenology, (b) neurophysiology and EEG, (c) neurochemistry, (d) neuropharmocology, (e) clinical diagnostic testing.

This type of examination will be used beginning with the December, 1957, examination.

The American Board of Psychiatry and Neurology, Inc.—After examination in New Orleans on March 18 and 19, the following candidates were certified in Neurology by The American Board of Psychiatry and Neurology:

Anderson, William W., San Francisco
Banker, Betty Q., Boston
Berris, Harold, Minneapolis
Carter, Charles Conrad, Portland, Ore.
Collings, Harold, Jr., Denver
Landau, William M., St. Louis
*Manfredi, Harold Michael, Cicero, Ill.

Matzilevich, Benjamin, Natick, Mass.
Mosier, Jack M., New Castle, Ind.
Reilly, James A., Jr., New York
Talbert, O. Rhett, Charleston, S. C.
Teasdall, Robert Douglas, Baltimore
Toupin, Henri M., Jamaica Plain, Mass.
Zier, Adolfo, New York

* Asterisk denotes supplementary certification.

Books

Subarachnoid Hemorrhage. By John M. Walton, M.D. Price, $7.00. Pp. 350. E. & S. Livingstone, Ltd., 16 and 17 Teviot Pl., Edinburgh 1, 1956.

Subarachnoid hemorrhage is covered thoroughly in this new text on that subject. By a comprehensive review of the literature and by summarizing the findings in a large number of cases studied at the Royal Victoria Infirmary, all aspects are dealt with. Ample discussion is given to the etiology, clinical picture, prognosis, and neurological and pathological findings. One chapter is devoted to the correlation of clinical and pathological features.

Particularly good is the section concerned with the comparison of medical and surgical treatment. Here the author assesses the value of both forms of therapy. He discusses the pros and cons of surgery and attempts to draw a reasonable conclusion from the diverse, and at times conflicting, previous reports and from the group he is reporting.

The author reviews 138 fatal cases of subarachnoid hemorrhage in an attempt to determine the possible value of surgery in this group. These fatal cases represented 44 (2%) of the whole series. Of these, 46 (14.7%) died within 24 hours of onset of the illness, and it is doubtful that surgery could have helped any of these. Another 14 (4.5%) of the whole series died before the end of the fourth day of illness, and the author generously estimates that one-half of these might have been helped. Of the group remaining, 31 (10%) died after the fourth day as a result of the first hemorrhage, and 47 (15%) died of a recurrence of bleeding in the hospital. It was in these two groups that surgery might have been helpful. When these three groups are combined and the five cases in which surgery was precluded are omitted, a total of 80 cases remain in which surgery could have been considered. At autopsy seven cases were found in which surgery could not have helped, e. g., primary intraventricular hemorrhage; there was no evident site of origin or of aneurysm in an inaccessible site. If the remaining 71 cases had all been saved by surgery, the total mortality of the series would have fallen to 23%.

On the basis of autopsy findings which suggested (a) that in some cases the aneurysms would have been difficult to treat surgically, (b) that in others the brain was too damaged to sustain life, and (c) that, in addition, unforeseen complications would probably have further increased the mortality, the author infers that by appropriate neurosurgical intervention at best the mortality might have been reduced to between 30% and 35%.

Though he concludes that as yet there are no absolutely clear-cut criteria to indicate the place of surgery in the management of cases of subarachnoid hemorrhage, he agrees that surgical treatment is entering the stage of consolidation.

A technical outline of neurosurgical procedures is not within the scope of the book. As the author states in the preface, "This book has been designed from the point of view of the physician." Many of the sections are followed by a short, succinct summary. The material is well organized and clearly presented.

Epilepsy and the Law. By Roscoe L. Barrow and Howard D. Fabing, M.D. Price, $5.50. Pp. 177. Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 49 E. 33d St., New York 16, 1956.

This book, of 177 pages, including a 22-page special "Legislative Index," is the product of two years of work by Dean Barrow, of the University of Cincinnati College of Law, and Dr. Howard D. Fabing, chairman of the Legislative Committee of the American League Against Epilepsy. The major chapters concern (1) marriage license laws, including a summary of current knowledge on the genetics of epilepsy and a brief account of the history of such legislation; (2) sterilization laws; (3) driver's license laws, including a discussion of the Wisconsin statute—a recent and satisfactory method for handling of this problem—and details a model statute for enactment; (4) workmen's compensation laws, including a refutation of

employers' arguments against hiring an epileptic and a discussion of the modern forms of legislation intended to further the employment of handicapped persons generally. An outline summary chapter of findings and recommendations ends the burden of the book. Four appendices give needed information for anyone seeking to introduce legislation.

This book is a valuable social study. It may well be the basis and the stimulus for legislative reforms throughout the country.

DONALD J. SIMONS, M.D.

Examination of the Nervous System: A Student's Guide. By Albert Theodore Steegmann, M.D. Price, $3.75. Pp. 164, with 40 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1956.

This is a handy, compact book of 164 pages, which includes a clear explanation of the necessary techniques for bedside examination of some of the functions of the central nervous system. The author has directed his attention to medical students and made his directions concise and lucid, for which they will be grateful. The drawings and pictures are well done and well placed to illustrate points that are often difficult to explain briefly and keep such a manual small. The directions for taking a neurological history are good, and the author points out that the neurological history does not substitute for the general medical history but only elaborates on it at specific points. One could quarrel over making a statement for student consumption that a complete social history is not necessary for most neurological patients, as this portion of the history is often of great importance and should not be neglected.

The book is pocket size and reasonably priced and can be recommended to instructors for student use.

FLETCHER McDOWELL, M.D.

Placebo Response

A. A. BAKER, M.D., and J. G. THORPE, Ph.D., Sutton, Surrey, England

I. Introduction

During this century the number of potent pharmaceutical compounds available to the doctor has been rapidly increasing. In psychiatry the last five years alone has seen the introduction of several powerful drugs classified as "tranquilizers," each of which is a distinct advance on any previous compound. This situation has led to the need to develop accurate clinical trials, with statistical assessment of the results. These clinical trials have usually involved the use of a dummy, or placebo, similar to the drug under investigation. In theory any response obtained with patients taking the active principle but not in the patients taking the placebo should be due to the drug. In practice a number of interesting and unexpected results have been obtained. Thus, Wolf and Pinsky [4] (1954), comparing the effects of mephenesin and a placebo, found similar improvement with both, and even side-reactions occurred with the inert tablet. Hawkings and Tibbetts [1,2] (1956), in a series of papers, showed that the same percentage of improvement occurred when neurotic patients received an inert substance as with the therapy previously considered effective. The present paper reports a placebo response in which a significant improvement occurred with the use of an inert tablet, whereas the active drug had produced no effect. There is at least one likely explana-

tion of this finding, and it provides a useful example of the difficulties in this type of investigation.

II. The Experiment

We initiated a small research scheme to assess the effect of mepazine (N-methylpiperidyl-(3)-methylphenothiazine; Pacatal) on incontinence in deteriorated psychotic patients. Incontinence is relatively easily recorded, and a previous investigation has shown that significant improvement occurred following effective treatment of the causative psychosis. Two groups of 18 deteriorated psychotic patients were chosen for this research, most having spent 15 to 20 years in hospital. Other active treatment was stopped for three weeks prior to the start of the experiment, and a record was kept for each patient showing the daily and nightly incontinence. The incontinence scores for the last nine days of this three weeks were taken as criterion scores for the experiment, and these form Period I. A course of treatment with either mepazine or the inert preparation was then started, commencing with 25 mg. t.d.s. and increasing every five days by 25 mg. t.d.s. until 100 mg. t.d.s. was reached. The identity of the tablets used was known only to the hospital pharmacist. The first nine days of treatment constitute Period II of the experiment; the second nine days, Period III, and the third nine days, Period IV.

III. Results

The mean incontinence scores are set out in the accompanying Table. These mean scores represent the average number of days of incontinence for each of the four nine-day periods. The statistical significance of the changes are assessed by the use of a t-test for related means. From the Table it can be seen that the mepazine group

showed no significant change in the daytime and, although night wetting shows a significant improvement during Period III, this is not maintained in the final period.

The results of the placebo-treated group are very surprising indeed. We have some highly significant reductions in daytime wetting which were not present for the mepazine group. We believe that there is at least one simple explanation for this unexpected result. Although the two tablets are similar in appearance, if they are tasted, the inert one is sweet. Thus, in terms of

Mean Incontinence Scores for Four Periods of Nine Days Each and Statistical Significance of the Changes

Period	Placebo Group (N=18)		Mepazine Group (N=18)	
	Day	Night	Day	Night
I	3.555	3.500	3.055	3.222
II	2.110	3.166	2.722	2.555
III	2.444	3.000	2.277	2.166
IV	2.166	2.888	2.222	2.500
Differences Between Means for Periods				
I and II	0.01>P	NS	NS	NS
I and III	0.05>P>0.02	NS	NS	0.05>P>0.02
I and IV	0.01>P	NS	NS	NS

total experience, our control group received several small sweets daily from the nurses, while the other group received a bitter pill. As shown by Merry[3] (1956) and others, small changes which improve the personal relationship between the nurse and the patient will lead to improvement in the behavior of the latter.

IV. Comment

We would like to mention some of the difficulties we have experienced in recent months in attempts to assess the effects of various tranquilizers on incontinence and other forms of behavior in deteriorated psychotic patients. It is not always realized that what is known as the "double-blind" method of approach to this problem is an attempt to adhere more strictly to the scientific principle which is being used. This was formulated long ago by John Stuart Mill and states that when the addition of an agent is followed by the appearance, or its subtraction by the disappearance, of a certain event, other circumstances remaining the same, that agent is causally connected with the event. It is difficult, if not impossible, to ensure that other circumstances do in fact remain the same, though if they do not it is obvious that the causal relation cannot be established by this method.

Before discussing these circumstances, we must point out that any attempt to observe a form of behavior in our patients has often led to a change in that form of behavior. We have found it to be most marked with regard to aggressive behavior and its immediate consequences, but it has also applied to other forms of behavior. We have several times seen patients hide the evidence of their incontinence when an experiment was in progress who had never been known to do so before. This means, of course, that we are assessing behavior not as it generally occurs in the ward, but only under the special circumstances of the investigation.

Returning to the above scientific principle, we may first note that the active preparation may differ from the inactive one in a variety of ways over and above the presence or absence of the active ingredient. For example, one may be sweet and the other bitter, as described earlier, or one may be soluble in water and the other insoluble, and so on. Thus the subjective experiences of the patients taking the tablets may differ. Secondly, such things as the solubility of the tablets and their appearance when crushed provide leads to the nursing staff regarding which tablet contains the active, and which the inert, ingredient. We have found that only one satisfactory experiment of this type could be carried out at this hospital. On this occasion the ward sisters were told that we were trying out two forms of a new drug, and this they apparently believed. Once the results of the experiment were made public, however, further work along the same lines was prejudiced, as the first interest of the ward sisters now became that of finding out which was the inert tablet! If the nursing staff do know which tablet is which, this knowl-

edge (accurate or inaccurate) may influence their attitudes toward the patients under investigation. The patients receiving one form of the drug may then receive different nursing care from those receiving the other. If this is so, we cannot establish our causal relation.

Finally, one often reads in the literature that the person making observations on the effects of the inert or active preparation did not know which the patient was receiving. We have found, however, that this condition is difficult to achieve. Most of the tranquilizers produce obvious secondary changes in the patient, apart from their effect upon his or her mental state. Reserpine leads to a Parkinson-like picture, chlorpromazine (Largactil) to facial pallor, and mepazine to a dry mouth, and each of these effects becomes obvious to any observer. As any ratings of these patients are likely to be influenced by this knowledge, again our causal relation may be inaccurately established.

Suggestions have been made in the literature that papers recording the effects of new drugs should do so only if they are able to report suitably controlled clinical trials using an inert preparation for comparison. We wish to point out that such trials are not proof against the errors introduced by personal bias resulting from knowing which patient is receiving which drug, nor, as in our own experiment, are they proof against errors introduced by a faulty placebo. In psychiatry in particular, where the attitude of either patient or nurse may be of greater importance than the pharmaceutical effect of the drug, one should beware of feeling that because a clinical trial is adequately described in considerable statistical detail, the results are therefore more valuable.

V. Suggestions

At the outset it should be made clear that one can reasonably expect the first experiment in any hospital to be fairly successful if the nursing staff is told that two forms of a new drug are being investigated, if the

placebo is satisfactory, and if the assessments of the patients are objective. For subsequent experiments a different technique is required if the results are to have maximum value.

In the first place, the patients should be unaware that any experiment is in progress. In order to achieve this, it may be necessary in some experiments in which the behavior of the patients has to be observed, that this be done by means of a one-way screen. Secondly, it is necessary to ensure that the subjective experience of the patients is the same on taking the active preparation as on taking the inactive one. This can be achieved by a close comparison of the two preparations with regard to taste, smell, color, shape, size, and texture. Thirdly, it is important to ensure that the patients in the two groups receive identical nursing care and attention. It is difficult to see how this can be achieved if the nursing staff know that one group is being treated with a drug and the other with an inert tablet. One solution to this problem would appear to be the formation of a research unit staffed by research-minded personnel who were more interested in the long-term than in the immediate welfare of their patients. In this connection we must remember that our first concern is the treatment of our patients, and none should suffer in order to provide long-term research material. Our experience has been, however, that in the case of long-stay, deteriorated psychotic patients the extra attention they received through taking part in research schemes has helped them. Alternatively, the whole experiment could be duplicated in two wards, in one of which the nursing personnel are in favor of drug therapy and in the other habit training or some other therapy is preferred. In this way any effects of these divergent attitudes upon the nursing care and attention given to the patients would be controlled. Fourthly, all assessments of patients both before and after the experiment should be as objective as possible. These assessments should be relatively unaffected by the sub-

jective impressions and evaluations of the observer.

Even if this scheme of inquiry be followed, and the conditions laid down by the scientific principle we have chosen to employ are approached as nearly as possible, there remains the problem of the drug producing dramatic side-reactions, which will hardly ever occur in the control group. The probable effect of these side-reactions on the patient's subsequent attitude to the drug which produced it and also on his behavior must always be carefully considered in evaluating the results of this type of experiment.

VI. Summary

An experimental evaluation of mepazine (Pacatal) in the treatment of incontinence is presented. The incongruity of our results has led to a discussion of the more important of the difficulties in this type of research. We have found that the "double-blind" method of investigation has numerous defects which are usually disregarded. Suggestions are made on how best to remedy these defects, though a completely satisfactory answer appears difficult to achieve.

Sisters Doyle, Loan, Huddlestone, Siewert, Clarke, Bailey, and Morgan recorded the experimental data, in addition to carrying out their heavy nursing duties. Mr. Runham carefully guarded the identity of the tablets, and Dr. Charlton gave us permission to publish these data. Messrs. Warner and Co., Ltd., supplied the Pacatal and placebo tablets.

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Effects of "Tranquilizers" upon Pathological Activity in Psychotic Patients

II. Reserpine

ROBERT P. CUTLER, M.D., Evanston, Ill.; JACK J. MONROE, Ph.D., and THOMAS E. ANDERSON, Ph.D., Lexington, Ky.

Since reserpine was introduced, in 1953, numerous descriptions of its effects upon psychotic behavior have appeared in the psychiatric literature. Although most of the reports are highly laudatory,[1-6] some of the more recent studies have failed to reproduce the dramatic results which have been reported.[7,8] Nearly all of the studies attempted to measure the effects of reserpine in terms of changes in disturbed behavior. However, few investigators have used a preliminary observational period to specify the behavior to be studied and to establish base line measures for evaluating changes in behavior after drug administration was begun. Indeed, in some reports it is even difficult to determine what observations were made or what specific criteria of improvement were used. In addition, few investigators have analyzed the results to determine whether the observed changes in pathological activity were reliable or statistically significant.

It is noted that when studies were well controlled, and when objective instruments were used to make repeated observations on the same subjects, less pronounced beneficial effects were reported.[7,8] Although time involved in applying such individualized procedures may reduce the number of subjects which might be studied, size of sample population does not in itself assure either relia-bility or validity. Increasing the number of subjects does not necessarily compensate for errors that may be inherent in procedure. Thus, in testing the action of potent drugs where substantial effects are expected, reliable measures repeated on a few subjects will show the efficacy of the drug more surely than can less well-controlled observation of many subjects.

In a recent investigation of the effects of chlorpromazine upon psychotic behavior,[9] we attempted to avoid some of the difficulties and omissions mentioned above. It was concluded from that study, using doses of 600 mg. daily, that pathological activity in 12 psychotic patients was reduced significantly by chlorpromazine. At these dosages the reduction in such activity was due partly to a significant increase in somnolence during hours that were usually wakeful. This increase in somnolence, however, was not sufficient to account for all of the change in behavior, since hours of symptom-free behavior were also significantly increased.

In a similar manner, the purpose of the present study * was to investigate the effects of reserpine on psychotic activity. The study was designed so as to permit the analysis of any measured behavioral changes into two portions: that which was due to an increase in somnolence, and that which was due to reduction of pathological activity. As in the previous study, it was proposed

to analyze the relationship between pathological activity and somnolence observed during hours of the day when patients normally were awake. Finally, the results obtained from the use of reserpine were to be compared with those obtained from the use of chlorpromazine.

Methods and Materials

Observers and Subjects.—Twelve male psychiatric aides, with an average of 10.7 years of experience in handling psychotic patients, served as observers. They were given no information concerning the drug that was being tested or of the alternation of subjects on drug and placebo. The instructions for observing and recording patients' activities, as well as the uniformly optimistic attitude of observers toward drug therapy, were similar to those in the previous study.[8]

Thirteen chronic schizophrenic patients, who ranged in age from 28 to 64 years, with an average age of 47, were selected because each had shown daily behavioral signs of pathological activity over an observational period of at least three months. Seven were of the paranoid type, two of the hebephrenic type, two of the undifferentiated type, and two of the catatonic type. Length of illness ranged from 5 to 45 years, with an average of 21.7 years. Eight of the patients had been subjects in the chlorpromazine study, which had terminated four months prior to this study. During the course of their illness, all patients had received ECT and insulin therapy, and two of them had undergone lobotomy six years prior to this study. Except for the previous study mentioned, none had received any therapy beyond ordinary institutional care for four years prior to the experiment.

Experimental Design.—The procedures were quite similar to those of the earlier study.[9] After five weeks of observation and recording of pathological activity and sleep, the 13 patients were divided into three groups and thereafter referred to as Groups A, B, and C. Groups A and B, composed of five subjects each, were matched on the basis of level of pathological activity. Group C was composed of three subjects whose pathological activity was significantly less (or more variable) than that of the other patients. After this control period, Group A received reserpine for a period of 13 weeks, while Group B received placebos. This was followed by a nine-week period during which the conditions of Groups A and B were reversed. Group C was given reserpine throughout the 22 weeks of the experiment. Only the pharmacist knew which group of patients was on reserpine and which on placebos at any given time. Reserpine was given orally. An initial dose of 1 mg.

per patient on the first day was gradually increased over a five-day period to 5 mg. per day. Beginning with the sixth day, doses were individualized to avoid undesirable side-effects, and ranged from 4 to 7 mg., with an average dose for all patients of 5.36 mg. daily. The placebos were identical in appearance with the reserpine tablets.†

Measurement of Pathological Activity and Somnolence.—Reference is again made to the previous paper, in which detailed descriptions of methods can be found.[9] Pathological activity was defined as those signs of motor activity which were peculiar to each patient, as revealed by a review of his medical chart over a period of two months prior to the experiment, and as revealed by direct observation of each patient by psychiatric residents and ward nurses. The aides were instructed to observe each patient hourly, except from 12:00 p.m. to 6:00 a.m., and to note in the appropriate space on a score sheet the number-symbol of the symptoms listed for that patient which appeared during each hour of the day. These observations were carried out seven days of each week. The degree of pathological activity exhibited by each patient was determined by counting the number of hours per week in which one or more of his characteristic symptoms were observed. Standard sleep charts, with spaces for entries every half-hour for all 24 hours of the day, were filled in on each patient throughout the control and experimental periods. A somnolence score on each patient was obtained by counting the number of hours during the week when he appeared to be asleep. Direct comparisons between pathological activity and somnolence were made possible by converting raw scores of each into "standard deviation units," using the control data as the standard. Weekly mean changes in pathological activity and sleep induced by reserpine were plotted separately for each group of subjects. The results of the groups were then combined, and the statistical significance of mean changes induced by the drug were evaluated by using the *t*-test for repeated measurements on the same subjects.[10]

Of special interest was the relationship between somnolence and pathological activity during the hours of the day when patients normally were awake. For this analysis only the incidence of pathological activity and sleep were used which were recorded from 8:00 to 11:00 a.m. and from 1:00 to 4:00 p.m. Since these observations covered 42 hours a week, a score of symptom-free behavior for each patient was computed by subtracting his weekly total of activity and sleep from 42. Mean changes induced by the drug in each of these measures were tested for statistical sig-

† Reserpine (Serpasil) was supplied through the courtesy of Dr. J. Campbell Howard Jr., Ciba Pharmaceutical Products, Inc., Summit, N. J.

TABLE 1.—*Means and Standard Errors of Weekly Pathological Activity Scores During Control Period*

Patients	First Week	Second Week	Third Week	Fourth Week	Fifth Week	Median Score
Group A						
1	101	99	98	101	100	100
2	91	103	90	96	96	96
3	89	81	83	57	83	83
4	77	58	97	54	55	58
5	67	59	62	47	46	59
6	94	93	97	98	99	97
Group B						
7	86	91	91	90	97	91
8	88	95	74	87	97	88
9	77	70	70	80	91	77
10	66	49	51	68	90	66
Group C						
11	33	43	37	51	71	43
12	34	32	36	37	39	36
13	95	101	37	98	95	95
Mean	76.77	74.92	71.00	74.15	81.46	76.08
S.E. Mean	6.07	6.80	6.70	6.30	6.00	5.99

nificance, using analysis of variance techniques.[10]

The reliability of the psychiatric aides in recording observations was tested in the same way as it had been in the previous study.[9]

Other Observations.—During the control period, the following observations were obtained on each patient: body weight, blood pressure, urinalysis, and complete blood count. Throughout the experiment, these procedures were repeated, as follows: weight determination, once monthly; urinalysis, once weekly; complete blood counts, every two weeks, and blood pressure recording, one-half hour after each dose of medication or placebo.

Results

Reliability of Pathological Activity Scores.—Table 1 shows that the least active patient during the control period had a median activity score of 36, which was more

than five times the largest standard error (6.8). Pathological activity scores were, therefore, sufficiently elevated and stable enough at the beginning of the experiment to permit measurement and statistical testing of possible changes induced by drugs. Rank-order correlations[10] between observers, showing reliability of the scoring, ranged from 0.64 to 0.99, with a median ρ of 0.82. These coefficients met the usual standards of interrater reliability.

The number of different symptoms which characterized individual patients ranged from 2 to 7, with a mean of 3.8. A list of specific behavioral symptoms is shown in Table 2. The total number of symptoms listed for all subjects was 50. On 24 of

TABLE 2.—*Distribution of Signs of Overactivity Among Twelve Psychotic Patients*

No.	Overactivity Sign Rated	No. of Patients in Whom		
		Sign Appeared	It Was Chief Sign	It Was "Fringe" Sign
1	Paces the floor	6	6	0
2	Aggressive swearing	5	3	2
3	Rushes from place to place	4	2	2
4	Talks to imaginary figures	4	4	0
5	Gestures with arms and hands	3	1	2
6	Inappropriate laughing	3	3	0
7	Sings and whistles	3	0	3
8	Draws and scribbles on paper	3	1	2
9	Makes homosexual advances	2	0	2
10	Loud, noisy talking	1	0	1
11	Grinds teeth and grimaces	2	1	1
12	Throws objects	1	0	1
13	Stamps feet	2	0	2
14	Plays with penis	1	0	1
15	Kicks objects	1	0	1
16	Picks up pieces of paper, dirt, etc.	1	0	1
17	Picks at skin	1	1	0
18	Eats fast; "wolfs" food	1	0	1
19	Sweeps cracks with feet and hands	1	1	0
20	Hits people or jabs them in chest	1	0	1
21	Rocks while sitting or standing	1	0	1
22	Shoves broom aggressively	1	1	0
23	Beats head with fist	1	0	1
24	Shakes fist at personnel	1	0	1
		50	24	26

Fig. 1.—Mean changes in pathological activity induced by reserpine in 12 psychotic patients. Line of clear circles indicates values for Group A, on drugs during the first 13 weeks of the experiment; line of solid circles, values for Group B, on drugs during the last 9 weeks of the experiment; line of solid squares, values for Group C, on drugs throughout the 22 weeks of the experiment.
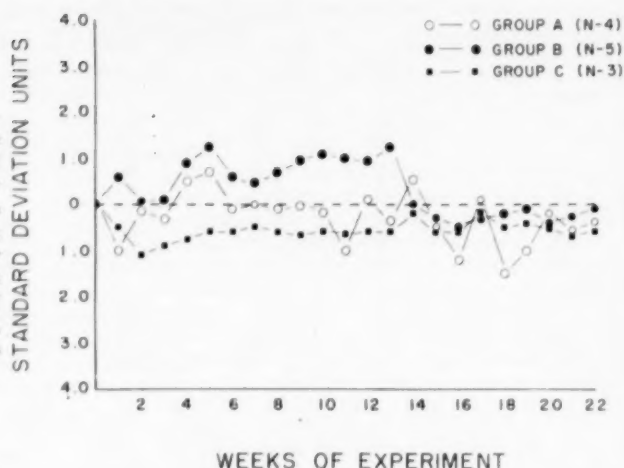
these there was essential agreement between observers. The remaining 26 symptoms were not consistently noted by multiple observers and may be considered "fringe symptoms," which, from the standpoint of measurement, represented inconsistent fluctuations in the patients' behavior. The 24 symptoms upon which the observers agreed, while representing 48% of the number originally "defined," accounted for 91% of the total pathological activity observed during the experiment.

Changes in Pathological Activity Induced by Reserpine (Fig. 1).—Group A, given reserpine during the first 13 weeks at an average dose of 4.50 mg. daily, showed no consistent direction of change in weekly means of pathological activity. Because of injury to one subject of this group, his scores were not included, although including them would not have altered the shape of the curve.

Group B, given reserpine during the last nine weeks of the experiment at an average dose of 5.75 mg. daily, showed a slight reduction in pathological activity while on the drug. This decrease in mean activity score was due to the marked drop in activity of one patient, who developed signs of severe Parkinsonism during the 15th week of the
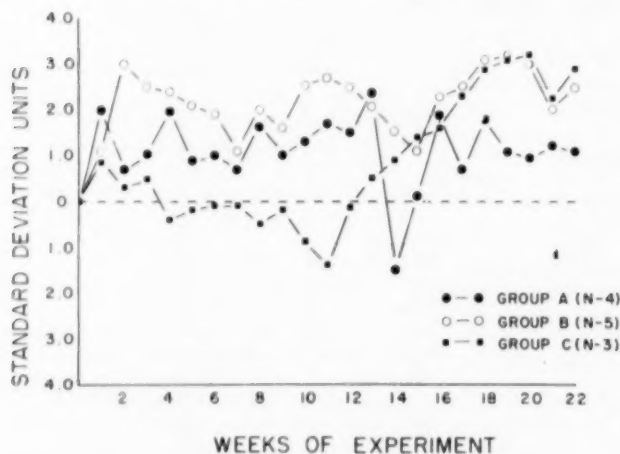

Fig. 2.—Mean changes in sleep induced by reserpine in 12 patients. Line of clear circles indicates values for Group A, on drugs during the first 13 weeks of the experiment; line of solid circles, values for Group B, on drugs during the last 9 weeks of the experiment; line of solid squares, values for Group C, on drugs throughout the 22 weeks of the experiment.

experiment. At no point did the mean reduction in activity for this group reach statistical significance.

Group C received reserpine for the entire 22 weeks; the dose averaged 5.23 mg. daily for 13 weeks, followed by an average dose of 7.00 mg. daily for the last nine weeks. The level of pathological activity for this group remained essentially unchanged throughout the experiment.

Changes in Sleep Induced by Reserpine.

Reserpine consistently increased hours of sleep in all three groups (Fig. 2). Group A showed a sharp rise in sleep during the 1st week of medication, which remained elevated for 13 weeks and then dropped abruptly to less than the predrug level when the drug was discontinued. Groups B and C showed comparable elevations in sleep while receiving the drug.

Drug-Induced Changes in Patients' Behavior During Normally Wakeful Hours.— The effects of reserpine upon pathological activity, sleep, and symptom-free behavior during a six-hour period of the day when patients normally were wakeful are presented in Table 3. Separately, none of the differences between control and drug means are statistically significant at the 0.01 level of confidence. However, a strong trend ($P<0.05$) toward increased somnolence during wakeful hours was demonstrated by

TABLE 3.—*Mean Changes in Hours Per Week* * of Pathological Activity, Sleep, and Symptom-Free Behavior During Normally Wakeful Hours Induced by Reserpine in Thirteen Psychotic Patients*

	Hours of Pathological Activity	Hours of Sleep	Hours of Symptom-Free Behavior †
Control	29.73	1.03	11.24
1	26.77	2.88	12.35
2	25.54	4.77	11.69
3	26.31	4.46	11.23
4	27.95	4.96	9.09
5	30.23	4.77	7.00
6	29.35	4.31	8.34
7	27.85	3.15	11.00
8	26.28	3.54	12.18
9	29.66	2.69	9.65
10‡	28.13	3.00	10.87
11	25.93	4.88	11.19
12	31.68	2.75	7.57
13	28.68	4.63	8.69

* Total number of hours per week in which observations were made was 42.
† Hours of symptom-free behavior are mean hours per week when neither sleep nor pathological activity was observed.
‡ Data on last four weeks of medication were based on eight subjects.

analysis of variance techniques.[10] No decrease in pathological activity was noted during the same period. The only consistent effect of the drug was sedation. In 10 of the 13 weeks of medication, reduction in pathological activity was canceled by increases in sleep, resulting in no increase in hours of symptom-free behavior. Actually, the absolute number of symptom-free hours was less during the drug periods than during the control period.

Comparison of Reserpine and Chlorpromazine.—Effects of reserpine and chlorpromazine upon total sleep in the 24-hour
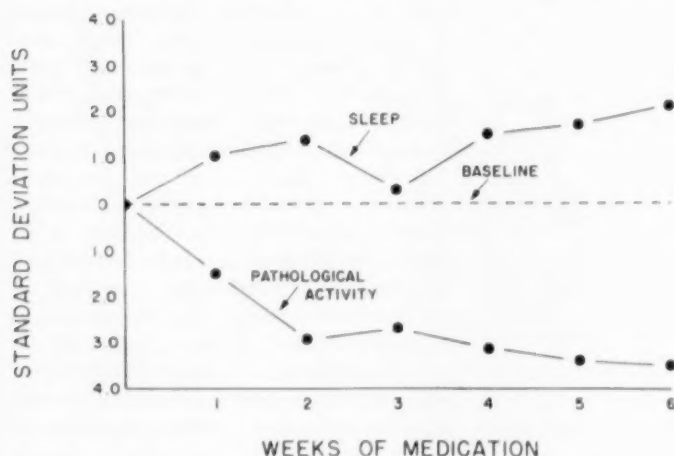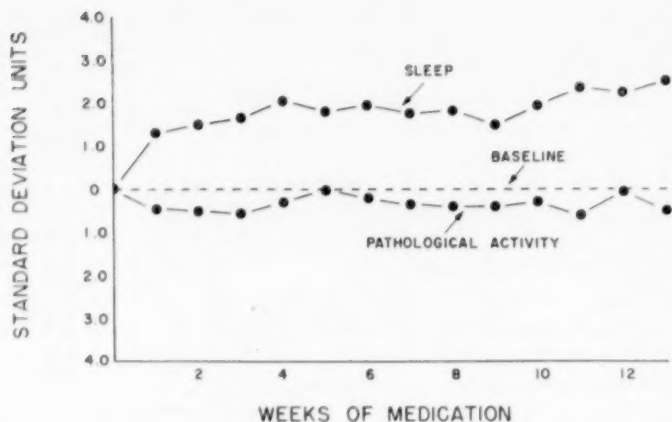

Fig. 3.—Mean changes in pathological activity and sleep induced by chlorpromazine in 12 psychotic patients.

Fig. 4.—Mean changes in pathological activity and sleep induced by reserpine in 13 psychotic patients. Data for the last four weeks were based on eight subjects.

WEEKS OF MEDICATION

day and upon pathological activity are shown in Figures 3 and 4. A comparison of the two Figures reveals that chlorpromazine significantly reduced weekly means of pathological activity ($P<0.01$) and significantly increased weekly means of sleep ($P<0.01$). Reserpine significantly increased weekly means of sleep ($P<0.01$) but had no significant effect upon pathological activity.

Following both drugs, consistent increases in somnolence occurred during hours of the day when patients normally were awake. Table 3 reveals that in the second week of medication with reserpine weekly means of sleep had increased from a control mean of 1.03 to 4.77 ($P<0.05$). The sedative effect following chlorpromazine, reported in a previous study,[9] was somewhat greater, where mean hours of sleep increased from 1.50 to 11.75 in the second week of medication ($P<0.01$). The increase in sleep following chlorpromazine was not sufficient to account for the decrease in pathological activity, since symptom-free hours were significantly increased under drug conditions ($P<0.01$). After administration of reserpine there was no such increase in symptom-free hours. Thus, if any reduction in pathological activity did occur, it was entirely accounted for by increase in sleep.

Side-Effects.—One patient, receiving 6 mg. of reserpine daily, developed signs of Parkinsonism during the second week of medication. A mild tremor of the hands became gross after 10 days and was accompanied by a labile blood pressure. These signs disappeared a few days after the drug was stopped. Aside from occasional tearing and rhinorrhea, no other side-effects were observed.

Comment

Although the findings of this study are at variance with numerous reports on reserpine in the psychiatric literature,[1-6,11-13] they agree closely with the results of an increasing number of studies.[7,8,14-16] which failed to confirm the marked beneficial effects of reserpine on pathological behavior. Success or failure to obtain beneficial effects from use of a drug is mainly dependent upon three factors: efficacy of the drug; choice of criteria of improvement, and characteristics of subjects. The population used in the present investigation was limited to chronic schizophrenic patients, and criteria of behavioral change were restricted to reduction in pathological activity and increase in somnolence. Furthermore, a sample of the most disturbed, hyperactive patients were selected for the study, regardless of age or duration of illness. Nevertheless, when present results are compared with those of other investigations in which similar patients were studied, and in which

amelioration of psychotic symptoms was the criterion of improvement, discrepancies are still apparent. Barsa and Kline,[12] reported some improvement in 80% of patients who had been continuously hospitalized for more than five years. Rinaldi, Rudy, and Himwich [11] found at least partial improvement in 82% of a group of chronic psychotic patients, the majority of whom were between 40 and 70 years of age, with long histories of hospitalization. The present investigators saw no conclusive evidence of unequivocal improvement in any of the 13 patients studied.

In general, it appears that the better-controlled, more objective studies show less dramatic results after use of the drug. In two studies, when the Ferguson Hospital Adjustment Scale was used to evaluate behavioral changes, only trends toward improvement in psychotic behavior were seen.[8,16] In three other studies in which the effects of the drug were measured with the L-M Fergus Falls Behavior Rating Scale no improvement was found.[7,14,15]

Many investigators have reported that when reserpine is given in large doses somnolence is increased. Hoffman and Konchegul [6] estimated that three-fourths of the patients who show an over-all response to the drug display some degree of drowsiness. Barsa and Kline [12] reported that sedation from the drug lasts only 3 to 10 days and may disappear without requiring reduction in dosage. The results of the present investigation support the findings of Hoffman and Konchegul, who observed that when adequate doses were maintained sedation continued throughout the period of medication.

Doses and length of treatment with reserpine vary greatly in different studies. Doses ranging from 1 to 10 mg. daily and lengths of medication ranging from four weeks to several months are reported. Mode of administration is both parenteral and oral. When the drug was administered intramuscularly,[4,12,13] dramatic results were usually reported. With oral administration, reports of effects have been conflicting, and

degree of improvement has seemed unrelated to size of dose or duration of medication. Rinaldi, Rudy, and Himwich,[11] using oral doses of 4 mg. daily over a four-week period, reported improvement in 32 of 39 psychiatric patients, whereas Penman and Dredge [14] gave psychotic patients oral doses of 8 mg. daily for 60 days without measurable improvement. We used oral doses of 4 to 7 mg. daily for 13 weeks, but noted no statistically significant reduction in pathological activity in chronic schizophrenic patients.

Summary and Conclusions

In a double-blind experiment, the effects of reserpine on pathological activity and sleep were studied in 13 hyperactive schizophrenic patients. Doses of reserpine were individualized and ranged from 4 to 7 mg. daily. Pathological overactivities peculiar to each patient were recorded hourly by psychiatric aides over a period of 22 weeks. Hourly sleep charts were kept over the same period. The recordings made of both activity and sleep, for hours when patients were usually awake, were analyzed separately from total recordings. Finally, the effects of reserpine were compared with those obtained in a previous study following administration of chlorpromazine at doses of 600 mg. daily.

At the specified doses, reserpine significantly increased hours of sleep. There was a strong trend toward increased somnolence during hours of the day when these patients were normally awake. Effects of the drug upon pathological activity were statistically negligible.

It is concluded that whereas chlorpromazine, as shown in a previous investigation, is effective in reducing the frequency of occurrence of defined symptoms of pathological activity, reserpine is not effective in reducing such symptoms. Both drugs, however, significantly increased total somnolence in the 24-hour day. The implication of these findings is discussed with reference to reports that have appeared in the literature.

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The Course of Childhood Schizophrenia

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Clinical disorders which are characterized by a prolonged and fluctuating time course provide particularly vexing problems for the evaluation of therapeutic results. Chance alone makes it inevitable that spontaneous remissions will coincide from time to time with almost any therapeutic measure if it be employed with sufficient frequency. When such chronic disorders occur in children, their complexity is further multiplied by the developmental process, with its own internal clock, which now races ahead, now slows down, and is likely to be deranged by the illness itself. Once again, it seems inescapable that steps in maturation will now and again follow the introduction of new treatment programs. The very eagerness of the investigator, as a physician, to relieve the suffering caused by the illness makes him all too ready to assign the changes observed to the agent he is administering at the time.

If there be any characteristic of childhood schizophrenia which is manifest in all clinical accounts, that characteristic lies in its long and fluctuating course. From the considerations advanced above, the puzzling phenomena of observed behavior can be regarded as the resultant of at least two interacting, irregularly oscillating determinants: (a) the somatopsychic or psychosomatic pathology, and (b) the developmental process, each reinforced or retarded by environmental factors. This very variability of the disorder sharply restricts the usefulness of individual case studies in the evaluation of treatment procedures. Each report, nevertheless, remains valuable, first, as an example of what can happen in childhood

schizophrenia and, second, in providing clues as to possibly effective techniques in treatment. But to conclude from one or a few cases that method X *is* beneficial merely illustrates the prevalence of the *post hoc* fallacy.

The obvious answer—and the only final one—to the measurement of therapeutic effectiveness lies in a properly designed, controlled study with schizophrenic patients assigned to treated and untreated groups by careful matching or random placement. Such studies are, however, more readily conceived than executed. The condition is itself relatively uncommon, so that few centers can accumulate sufficiently large series. It is difficult to maintain an "untreated" group, for parents understandably seek relief for their child, not the answers to scientific curiosity, even if they admit that only such answers can ultimately solve the problem. Moreover, clinicians themselves seem too easily persuaded that a given method is the correct one if it be based upon a conceptual foundation to which they are committed. Others contend that psychiatric studies do not lend themselves to quantification, each case being different; consequently, they continue to rely upon intensive study of individual patients, some of whom improve, as indeed the remission rate tells us they must.

It will be revealing no secret to admit that, at this point, the ideal controlled study remains to be done. Are we then without guidelines in making prognostic judgment or in attempting at least a preliminary evaluation of the efficacy of suggested therapeutic measures?

There exist in the literature a number of reports of the vicissitudes of outcome in cases of childhood schizophrenia followed over fairly long periods of time. A review

of the pertinent literature, in the light of the experience at the Children's Psychiatric Service of The Johns Hopkins Hospital, can provide at least the beginning of a "natural history" of schizophrenia in childhood, against which contentions of improvement ascribable to treatment can be measured.

Before we can attempt a critical evaluation of available follow-up studies, it is necessary to face the rather considerable problem provided by the wide variability in the conceptions of childhood schizophrenia and, consequently, in the criteria for diagnosis. The accumulation of reliable information about the course of a disease process and its modifiability by treatment presupposes comparability in the cases described as examples of the disorder. Could any significance be ascribed to a discourse on the treatment of "meningitis" if no attempt were made to cite species and type? It may be do not know in the former instance, as we argued that the analogy is inapplicable; we do in the latter, the etiologic agent or agents. But would we any longer discuss the prognosis of "mental deficiency" without distinguishing the many syndromes which we can differentiate on clinical grounds alone with as yet little or no clear idea as to their cause? The very success in distilling out recognizable entities has made most clinicians chary of generalizations about the still unclassified residuum of mental deficiency. Is not even greater caution indicated in the only lately charted field of childhood psychosis?

A brief historical note may serve to emphasize the recency of the renaissance of interest in childhood schizophrenia and the persisting need for careful description and analysis. Paradoxically, though the term *démence précoce* was coined in 1860 by Morel[1] for a psychosis in a 14-year-old boy, certainly as much child as adult, relatively little attention was given to the form of the earliest manifestations of dementia precox by subsequent students of the disorder. Kraepelin[2] is often cited as stating that onset occurred before the age of 10 in

3.5% of 1054 patients he reported. But on a closer analysis of his account we find him describing "a group of patients in whom already from childhood upwards a considerable degree of psychic weakness existed, although the more striking morbid phenomena only later, perhaps in the third decade, became noticeable and now led to fairly severe dementia."[3] He referred to these as cases of "engrafted" hebephrenia *(Pfropf-hebephrenie)*, stressing the fact that "dementia praecox was in a certain manner grafted upon an already existing disease." Thus, we find that these cases were for the most part retrospectively diagnosed, and the differentiation between premorbid personality trends and the onset of psychosis per se was a matter of "uncertain and arbitrary"[3] judgment from the history supplied. Kraepelin appears to have had little actual experience with children as patients except for a number of cases of idiocy and imbecility, which he regarded as the end-state of an unrecognized dementia precox, on the basis of mannerisms and bizarre behavior. Bleuler,[4] with a more specific concept of the characteristics of schizophrenic psychopathology, stated in 1911:

With relatively accurate case histories, one can trace back the illness to childhood, even to the first years of life, in at least five percent of cases. In this process, we completely disregard the anomalies which do not have a distinctly schizophrenic character.

The limitations of his experience with children are apparent in the further comment: At the present time, we know of no differences between the infantile and other forms of the disease . . . . The prognosis of those cases in which the onset of the illness occurs before puberty does not appear to be too poor for the next few years. What happens to them later I do not know . . . . However, the case histories of adults admitted to the hospital show that at least part of these early cases relapse and then usually become markedly deteriorated.[4]

Perhaps the first specific consideration of childhood schizophrenia as a separate category dates from the earliest papers (1905-1908) of de Sanctis, who suggested the term dementia praecocissima to designate this clinical subdivision. It became evident,

however, that de Sanctis included not only cases of childhood schizophrenia as most of us employ the term today, but as well others with chronic brain syndromes and severe mental deficiency.[5] Such scrap basket diagnoses, the loose usage of "childhood" to include onset as late as 16 or 17 years of age, and the predominant preoccupation of psychiatrists with hospitalized adults, each contributed to a growing disbelief in the reality of schizophrenia in childhood. As recently as 1942, Bender commented[6]:

There are those who do not believe in childhood schizophrenia, not having seen a case. At the best, none of us has seen very many cases in which we could make a definite diagnosis, not knowing the acceptable criteria. There are others who, having seen certain types of mental disorders in children, prefer to call them schizophrenic-like psychoses of childhood.

No more than 10 years later we find Despert stating[7]:

Although there are still people who believe that there is no such thing as schizophrenia in childhood, generally speaking we might say that the concept of childhood schizophrenia has passed from non-recognition to over-recognition.

Among the unconvinced minority remain such authors as Katan[8] who contend, on theoretical grounds, that schizophrenia cannot occur in childhood.

The contemporary era of interest can be said to date from the end of the third decade of this century. Early studies were far from convincing and were hotly contended. For example, in the same volume of the *American Journal of Psychiatry*, Burr,[9] then professor of mental diseases at the University of Pennsylvania, declared: "The youngest case of hebephrenic dementia praecox of which I have records occurred in a boy not quite 15 years of age," and Brill[10] described two patients, one 4½ and one 6 years, whom he considered catatonic. He referred to others, not elaborated upon, whom he had also seen. Critical scrutiny of Brill's capsule case histories, however, leaves considerable doubt as to the accuracy of the diagnosis of catatonia, even though one of these patients was later hospitalized at the age of 19 as a schizophrenic. More precise consid-

eration of the problem of childhood schizophrenia began to emerge with such papers as that by Kasanin and Kaufman.[11] These authors, surveying admissions to the Boston Psychopathic Hospital from 1923-1925, found 21 of 65 children admitted with the diagnosis of schizophrenia. Of these 21, they considered 6 as "typical" schizophrenics, but the age of onset of several indicates a rather elastic concept of childhood. (For a more complete bibliography of early case reports, see Bradley[12] for the world literature up to 1941 and Goldfarb and Dorsen[13] for the literature in English through 1954.) Clarity began to emerge with Potter's[14] proposal of a general set of diagnostic criteria, which attempted to take into account the developmental level and intellectual idiosyncrasies of childhood as factors which necessitated a modification of classic notions of symptomatology. The first effort to describe clinical subdivisions among this heterogeneous group of disorders appeared with the contributions of Ssucharewa[15] and Grebelskaja-Albatz,[16,17] who proposed a division by mode of onset (acute or insidious) which was felt to have prognostic importance. Despert[18] later discriminated a third mode of onset: insidious with acute exacerbation, environmentally precipitated. Lutz, in a scholarly study of the world literature through 1936,[19,20] was able to locate some 60 cases that had been reported as instances of childhood schizophrenia. He took age 10 as the dividing line between childhood and adolescence as a stringent requirement to limit his consideration to prepubertal cases, a step which eliminated 30 cases. He reviewed the remaining reports by rigorous criteria in order that he might discern the distinguishing features presented by those children for whom the diagnosis was beyond question. The criteria employed were those of Bleuler and Homburger; the latter had stated that the most critical factor in making the diagnosis was the course of the disorder.[21] By these cautious standards, there remained only 14 cases in which one could speak with certainty of schizophrenia

(mit Sicherheit von einer Schizophrenie zu sprechen). He had, for example, dismissed the cases of de Sanctis, since many were clearly instances of organic brain syndromes (organische Gehirnstörungen); he accepted only Cases 4 and 5 of Potter,[14] though he considered Cases 1 and 2 as presumptive (wahrscheinlich). (The remaining cases were compiled from 3 by Weichbrod, 2 each from Vogt and Schnabel, and 1 each by Higier, Grebelskaja-Albatz, Tramer, Strohmayer, and Meier.) He added six cases of his own, which are reported in detail. He then summarized the observations on the series of 20 in terms of cause, frequency (less than 1%), course, manifestations, differential diagnosis, treatment, and prognosis: (Die Entwicklung einer kindlichen Schizophrenie verläuft durchwegs ungünstig, ungünstiger als der Durchschnitt der Fälle bei Erwachsenen—the development of childhood schizophrenia is always unfavorable, more unfavorable than in the average case among adults). His papers remain landmarks in the early literature on the subject.

The first major contribution to the differentiation of specific clinical types within the group of childhood schizophrenias was Kanner's delineation in 1943 of "early infantile autism."[22] He defined an entity whose pathognomonic features are extreme aloneness and an obsessive insistence on the preservation of sameness, with secondary symptoms in the spheres of communication and motor behavior.[23] Its onset, usually by the end of the first year of life and not later than the second, marks it as the earliest of the forms of schizophrenia.[23] The psychiatric literature from 1943 to 1948, while including additional contributions from Kanner,[25-26] is marked by a paucity of confirmatory papers by others, a finding which suggests reservation in accepting autism as an entity. Since 1949, however, the diagnosis has appeared with ever-increasing frequency[27-52]; the concept, now rather widely accepted, is being more and more widely applied, with a tendency to-

ward dilution of its specificity.[23] It remains a classic example of the elucidation of a clinical entity through careful observation and analysis. It distills out of confusing heterogeneity a circumscribed syndrome, separable by symptoms and course from other psychotic states in children.

Kanner's pioneering effort was followed by Mahler's description of the "symbiotic infantile psychosis."[28,29] It is characterized by a later onset and distinguished by symptomatology centered about a desperate effort to avert the catastrophic anxiety of separation. Mahler and Settlage[53] have recently proposed a more elaborate classification with (1) early infantile autism, divided into (a) "resistive and negativistic" and (b) "pliable and passively conforming," and (2) symbiotic infantile psychosis, divided into the subtypes (a) "parasitic-clinging," (b) "searching for symbiosis," (c) "acute symbiotic," and (d) "secondary autism." Despite the theoretical clarity of this proposal, whether these subcategories will ultimately prove clinically useful remains a matter for experience to decide.

Meanwhile, Lauretta Bender, whose experience with childhood schizophrenia is by far the most extensive in this country, if not in the world, had been pursuing a different conception of the disorder. She had offered the formulation that it is "a clinical entity occurring in childhood before the age of 11 years which reveals pathology at every level and in every area of integration and patterning within the central nervous system, be it vegetative, motor, perceptual, intellectual, emotional, or social."[6] The emphasis is biological; the fundamental pathologic process is stated to be a diffuse encephalopathy[54] for which no confirming anatomical evidence is described. Bender has currently suggested a classification into clinical types: (1) the pseudodefective or autistic regressive type; (2) the pseudoneurotic or phobic, obsessive-compulsive, hypochondriac type, and (3) the pseudopsychopathic or paranoid, acting-out, aggressive antisocial type.[55] So large is the number of cases (850) reported

from the Bellevue group,[55] unparalleled in the experience of other clinics whose special interest in the problem makes them centers for referral of psychotic children, that inevitable questions arise as to whether the diagnostic concept is not so broad that many cases are included which others would not consider to be schizophrenic.

The recent period has seen other delineations of clinical types which may be regarded as falling within the framework of childhood schizophrenia, such as Bergman and Escalona's "children with unusual sensitivity to sensory stimulation"[56] and Ekstein's [57-59] "borderline" psychosis (also referred to as "schizophrenoid"). The wheel seems to have come full turn with the appearance of a concept that recalls de Sanctis' dementia praecocissima, but even more broadly conceived. Rank has introduced the notion of the "atypical child," by which "we refer to more severe disturbances in early development, which have been variously described as Heller's disease, childhood psychosis, childhood schizophrenia, autism, or mental defect."[60]

To include Heller's disease—with its termination in irreversible dementia and its histologically demonstrable cortical pathology[61]—and mental defect (!) in the same category with childhood schizophrenia—itself suspect of being a somewhat heterogeneous group of disorders—can serve only to confound confusion. It is as if we were to urge a return to "brain disease" as a category and include therein the multiplicity of neoplastic, vascular, toxic, and traumatic disease states which have in common only their predilection for nervous tissue; imagine, then, the futility of efforts to formulate prognosis or plan treatment. Yet this is precisely what the concept of atypical development proposes for psychotic states in children. Nor is Rank's point of view that of her group alone. Szurek,[63] reporting the consensus of his co-workers at Langley Porter clinic, states:

We are coming more and more to the opinion that mild, moderate or even severe mental deficiency and organic brain disease can be complicated by severe mental disorder. . . . we are beginning to consider it clinically (that is, prognostically) fruitless, and even unnecesary, to draw any sharp dividing lines between a condition that one could consider psychoneurotic and another that one could call psychosis, autism, atypical development or schizophrenia.

There is no intention here of glossing over the very considerable problems in differential diagnosis.[64-65] Weygandt,[66] as long ago as the turn of the century, recognized the occurrence in patients with severe mental deficiency of symptoms paralleling those observable in schizophrenics. This, however, does not argue for the identity of diseases with overlapping symptomatology. The careful examination by Kallmann et al.[67] of genetic evidence for linkage between mental deficiency and schizophrenia by means of twin studies led them to the conclusion:

Our findings definitely indicate that the endogenous forms of schizophrenia and mental deficiency are based on different factors which are specific and not related to each other.

Currently, there are a number of efforts to enhance differential diagnosis, such as to formulate more specific testing procedures those of Ritvo and Provence,[68] Provence,[69] and Bender and Helme.[70] Other experienced workers are attempting to describe the psychological core of the disorder; Rabinovitch[71] has introduced the concept of "dysidentity," which he considers the fundamental psychopathologic process; Despert[7] has offered the definition of childhood schizophrenia as "a disease process in which the loss of affective contact with reality, or failure to develop affective contact, is coincident with or determined by the appearance of autistic thinking and accompanied by phenomena of regression and dissociation." She sharply indicates the importance of differentiating schizophrenic from obsessive-compulsive states.[72]

At present, most workers would agree with Hirschberg and Bryant[64] when they point out: "In childhood schizophrenia, we are not dealing with a separate and distinct clinical entity; rather, we are dealing with a group of related and overlapping clinical syndromes." The task would seem to be one,

as Kanner[72] has worded it, of "a sober evaluation and integration of the knowledge so far attained and more knowledge yet to be gained. This will probably come best from an attempt to study and separate the syndromes which present themselves and from an assessment of the manner in which centrifugal and centripetal factors fuse and blend—or fail to fuse and blend—in each individual patient" (compare also Despert and Sherwin[97]).

This rather considerable, though necessarily incomplete, excursion into unresolved problems besetting the diagnosis of childhood schizophrenia serves to emphasize the major difficulty in the analysis of follow-up reports. Despite the lack of uniformity in criteria for diagnosis, most accounts fail to specify with precision the standards employed. Vagueness in this area is, unfortunately, further compounded by failure, in many instances, to indicate the meaning given to categories of improvement and non-improvement. Nevertheless, despite these serious limitations, the available data provide at least a rough guide to the course of the various syndromes that comprise this group of disorders and a preliminary indication of their responsiveness to various therapeutic approaches.

Kraepelin, in his classic text, failed to mention any instances of recovery in the childhood form of dementia precox.[2] He considered two possible outcomes: one leading to severe idiocy; the other, to the more typical adult forms of the disorder. His evaluation of prognosis has, however, to be considered in the light of his conception of the basic process in this "disease," which, according to him, terminated inevitably in dementia; if it did not, the diagnosis had to be reconsidered. Bleuler's more meliorative note, already referred to,[4] that prepubertal cases do not appear to do too poorly "for the next few years," was based on limited opportunity for follow-up and is offset by his opinion that, when relapse occurs, childhood schizophrenics "usually become markedly deteriorated." Such childhood

schizophrenics as were included in de Sanctis' dementia praecossima terminated for the most part in irreversible idiocy; once again, this seems implicit in the diagnosis itself.[5]

The study by Kasanin and Kaufman[11] included six cases considered by the authors to be "typical schizophrenia"; two, *Pfropfhebephrenie*, and five, "reactive psychosis." Of the first group, three made some degree of recovery; of the second, none, and of the third, all. However, all that was definite about the "recovered" cases was that they had been able to leave the hospital; their subsequent fate was unknown. Ssucharewa[15] reported 25 cases under 13 years of age, 20 with insidious and 5 with acute onset. All but three of the former group had normal I. Q. scores, but certain of the cases suggest organic syndromes. Outcome, unfortunately, is not clearly specified but appeared to have been uniformly poor for the period (?) of the study; the main distinction between the two groups lay in the more rapid deterioration of those with acute onset. Bradley described the conclusions of a later paper by Sukhareva (Ssucharewa) and Kogan[74] in the following terms: "None of their patients had a complete remission. The disorder left a slight defect in one-third of the children, moderate in one-third, severe in the remainder." Grebelskaja-Albatz reported 22 children schizophrenic by the age of 8 years. Of the nine cases with acute onset, all presented a fulminating course that terminated in mental retardation of varying degrees of severity.[16] Of the 13 cases with insidious onset, only one appeared to have recovered sufficiently to attend a normal school.[17] Length of the follow-up contact is uncertain. Lutz,[19] basing his evaluation on 14 cases in the literature and 6 in his own experience, commented:

Der Ausgang ist bei den bis heute beobachteten Fälle ausnahmlos ungünstig. Oft müssen diese Kinder als Pflegefälle in Irrenanstalten versorgt werden und leben dort als geistige Ruinen, bis eine interkurrente Krankheit ihrem Dasein ein Ende setzt. Es fehlen noch genaue Beobachtungen über den weiteren Verlauf solcher Psychosen. (The outcome in the thus far observed cases is without

exception unfavorable. Often these children must be cared for as custodial cases in mental hospitals and live there as spiritual ruins, until an intercurrent infection brings their existence to an end. We lack sufficient observations on the further course of such psychoses.)

Despert's paper,[18] the most extensive in the American literature of the 1930's, and a model of clarity, described the course of 29 children hospitalized at the New York State Psychiatric Institute between 1930 and 1937 and followed for one and one-half to six years. Nine were less than 7 years of age on admission, and twenty, between 7 and 13. Of the seven with acute onset, six "rapidly deteriorated" and one achieved "partial restitution" and "relative adaptation." Of the 16 cases with insidious onset, 3 rapidly deteriorated, 12 showed a chronic course with "ultimate lowering of the ideoaffective level," and 1, a chronic course with one exacerbation. Despert added a clinical description of a third type of onset: "insidious with an acute episode." Of the six children in this category, two achieved remission with adaptation, three displayed gradual lowering of the ideoaffective level, and one rapidly deteriorated. She regarded anxiety as a bad prognostic sign; of the 11 with this as a marked feature, 10 deteriorated rapidly. Despert stressed the psychopathologic significance of "dissociation between language sign and language function." In a subsequent review[75] of this material, Despert supplied important additional details on the age, prepsychotic personality, etc., of these children.

Lurie, Tietz, and Hertzman,[76] in analyzing the first 1000 cases at the Child Guidance Home, evaluated 20 as psychotic, 13 of whom were schizophrenic. There were eight cases with acute onset, three with acute onset on an insidious background, and two with insidious onset. Of the total group of 13, only 1 was able to make an adjustment in the community during the period of follow-up (1-13 years). Potter and Klein[77] reported the course of 14 schizophrenic children whose illness began between 4 and 12 years of age. Four showed some improve-

ment at discharge, but three of these subsequently followed a downhill course. The authors concluded: "The outcome of the schizophrenic reaction group is exceedingly poor." Creak[78] reported 35 psychotic "children," of whom only 9 were 12 years or less at the time of onset. Of this latter group, the outcome was clearly poor in three, not specified in three but presumably poor in these as well, and good in three. Among the last cases, however, "Heather N." and "William B." were of a reactive character and "Basil L." questionably psychotic. Thus, in reviewing case reports through 1940, Bradley sadly concluded[12]: "The prognosis of childhood schizophrenia appears to be uniformly bad."

With the 1940's, however, there appeared a much more hopeful view of the prospects for these children. Cottington,[79] in describing β-erythroidin-modified pentylenetetrazol U. S. P. (Metrazol) shock treatment, maintained that some improvement was observable in six out of seven cases. The data presented, however, fail to support the conclusions in a study of extremely short duration. A second paper[80] on the same case material, enlarged to 15, reported 10 patients "definitely improved," of whom 7 showed "modification of behavior." The criteria employed for diagnosis were apparently Bender's, but those for evaluation of change were simply not specified by the author; the reader is left in the dark as to how to assess this work. A much more significant study was that by Lourie, Pacella, and Piotrowski,[81] who evaluated the cases of 20 children, schizophrenic by Potter's criteria,[14] ranging from 4 to 12 years of age at onset and followed for 4 to 11 years. Three of these cases, indistinguishable from the others initially, later developed signs of organic pathology and were consequently regarded as cases of symptomatic rather than true schizophrenia. Of the 17 "true" cases, 4 achieved an apparently normal adjustment in the community, scholastically as well as socially; 5 made a "fair to borderline" adjustment; 3 developed "typical adult schizo-

phrenia," and 5 failed to show any change or deteriorated. No clear relationship is apparent in the data between mode of onset and outcome, though acute onset early in life led to the worst result. The authors commented soberly:

Recoveries or remissions showed no definite correlation with any type of treatment, direct or indirect, though the relation between direct psychotherapy or environmental change in individual cases seems evident. In half the cases found to be doing best in follow-up, recovery or remission was apparently spontaneous.

This investigation remains one of the few solid contributions available in the literature.

Despert [82] described her experience in outpatient psychotherapy with seven schizophrenic children; in the short period of her study (three months to two and one-half years) she noted decided improvement in three, slow progress in two, and uncertain or poor results in two. She concluded that outpatient therapy for such children may be of advantage because of the preservation of contacts with home (a conclusion directly at variance with that of Bettleheim,[83] who urged the importance of severance of the relationship between mother and child through residential treatment as the key to successful therapy). Chess and Rubin [84] reported nine children treated at a child guidance clinic and followed up to five years. The authors indicated that the project seemed worthy of further pursuit but made no claim of major gains through psychotherapy. In some of the cases cited, some argument is possible as to diagnostic allocation. Bender and Gurevitch [85] reported five young schizophrenic children treated with psychotherapy, three of whom also received electroconvulsive treatment. Of the five, four showed "distinct improvement" during the several years of the study. Szurek,[63] summarizing his clinic's psychotherapeutic experience with over 100 children (but one should recall his earlier comment about diagnostic specificity in this group), declared that 14 "can be counted on as well or as very markedly improved. They are now in school and have been living at home for several years and progressing rather well."

Williams and Freeman [86] evaluated 12 children they considered as schizophrenic (criteria unspecified) and "treated" with lobotomy. Two died postoperatively. Four were mute preoperatively; one of these acquired "a few words" after the procedure. Their main contention for this mutilating operation is that it reduces "destructive hyperkinesia"; not one of the patients achieved a normal life, though the task of nursing personnel was simplified. Sackler et al.[87] reported on 19 schizophrenic children (Bender's criteria), 13 of whom received histamine therapy. All of the cases had displayed "overt pathology" by the age of 4 years and were chronically ill. It was claimed that 12 out of 13 showed "improvement," but its nature and its duration are not clearly indicated.

The papers of the 1940's and early 1950's might be summarized in the following fashion: They are in agreement in finding an appreciable percentage of remissions among childhood schizophrenics, certainly as contrasted with the prevailing pessimism of the 1930's. Whether this reflects the results of earlier detection, better general treatment measures, or an extension of the diagnosis to cover cases of a milder nature, it is not possible to decide. Because of the small number of cases (5 to 30) followed in each of the reports in both eras, it is entirely possible that the differences are more apparent than real. The available information justified only the statement that remission could occur but did not permit a reliable estimate of its likelihood. More accurate prognostic judgment had to await the careful follow-up of larger series of cases; this task was dependent upon the accumulation of experience at those centers with long interest in the problem under the continuous direction of the same investigators; namely, Bellevue, under Lauretta Bender, and Johns Hopkins, under Leo Kanner.

The larger of the two major studies now in progress is that by Bender and her associates.[88] She has presented some preliminary results of an analysis of the subsequent

careers of 350 children diagnosed as schizophrenic between 1934 and 1946 and followed from a minimum of 5 to a maximum of 15 years later. There were 143 shock-treated patients (43 with Metrazol, 100 with ECT) and 50 children not so treated, who formed the first groups to be evaluated. Of the former 143, she was able to trace 120. We are told that 104 of these were seen at one time or another by other psychiatrists, who considered 69 of them to be schizophrenic (66%), 16 mentally deficient (15%), 10 to have personality disorders (10%), and 9 other psychoses (9%). When 26 of the 35 in the last three categories were reexamined by a Bellevue research staff, 22 were diagnosed as schizophrenic; 16 others, part of the original group of 120 but not examined elsewhere, were also found to be schizophrenic by Bellevue criteria. Thus, 107 of 120 childhood cases (89%) were diagnosed as schizophrenic by Bender's group 5 to 15 years after the original diagnosis had been made. This Bender considers confirmation of her concept of childhood schizophrenia.

We can agree with this contention insofar as the persistence of a schizophrenic behavior pattern into adolescence, when criteria for its recognition are presumably more widely accepted, attests to a continuum between the two forms of the disorder. On the other hand, unless we believe that once schizophrenic, always schizophrenic, we can conceive of remission or recovery without the persistence of a clinically detectable residuum. It is important to note, in contrasting diagnosis elsewhere (66%) with that at Bellevue (89%), that the criteria employed by Bender's group do not include a requirement that the patient be psychotic, and may be influenced by a prior diagnosis at their own hospital. This may account for the higher percentage of diagnostic "confirmation"; it also suggests the need for a cautious evaluation of the high percentage of schizophrenic progenitors (40%) reported among the families of their children. This finding, for example, contrasts sharply with out own [87] in the families of 100 autistic children (5%). Psychotic or neu-

rotic states, in the Hopkins study, were explicitly restricted to disorders that led to hospitalization and/or psychiatric care.

As to outcome, Bender reported that two-thirds of the shock-treated group had required state hospital care after their stay at Bellevue, one-third continuously. At the time of the study, 50% were "in the community." "Twenty-five percent of the 50 now in the community are showing fair to good adjustment." (I presume "50" is meant to be "50%." It is later stated that "one fourth of the 143 shock-treated patients are making fair to good adjustment.") This result was contrasted with the outcome of 50 patients, not treated with shock, who were considered a "control" group. We are told that two-thirds were subsequently sent to state hospitals, one-third chronically, figures identical with those preceding; however, only two (4%) were making a "fair to good" adjustment. This difference is cited as an indication of the beneficial effect of ECT on prognosis. Unfortunately, the "control" group is largely (two-thirds) comprised of children whose parents refused treatment; the attitudes underlying this decision may very well be significant determinants in outcome. In view of the small number in the far from completely comparable "control" group and the great similarity of the course in other respects, the data supplied do not demonstrate any clear superiority for the treatment method.

One is left in further doubt as to the evidence for the claim for ECT in a later paper [55] that it results in "specific improvement in all but a minority" of treated childhood schizophrenics. If we examine, for example, the psychological studies of des Lauriers and Halpern [90] carried out on the very group of children whom Bender treated, we find these comments: ECT has "broken down all the superadded structure, the neurotic and anxious features, and there now appears in strong relief a clearly defined picture of schizophrenia. . . . There is no improvement in the mental continuum, there is no change in reasoning and judgment, the tendency to accept incidental and

far-fetched issues as important is still present . . . a general flattening of affect." The authors noted, somewhat wryly, that if ECT had done nothing else, it had served to clarify diagnosis, on post-, as opposed to pretreatment, testing. Other psychological studies at Bellevue [91] have demonstrated a lack of detrimental effects by ECT on intelligence, etc., but to show that it does not hurt hardly establishes the fact that it helps.

Moreover, Clardy [92] and Clardy and Rumpf [93] contend, with no less vigor, though with little more proof, that ECT has a bad effect and is dreaded by the patients themselves. Clardy reported 30 schizophrenic children, followed for 1 to 14 years. Group I (17 cases) differed from Group II (11 cases) in that the former had delusions and hallucination, but not the latter. Group III (two cases) differed from Groups I and II in manifesting less severe loss of contact. Of the first 17, 9 were "much improved" or "improved"; 8 of the second 11, and 1 of the last 2, at the time of the report. It is stated that the 10 who had received ECT became worse. The high percentage of favorable change noted stands in contrast with that in all the other papers in the literature. It is difficult to know just what is meant by the categories of improvement. Poor editing has resulted in manifest contradictions within the paper (I found eight unimproved, five improved, and four much improved in Group I, but elsewhere in the paper the figures are given as six, seven, and four; other errors can be noted). The second paper from Rockland State Hospital [93] described 32 patients "with schizophrenic manifestations," 30 of whom had received ECT at Bellevue. (Does this imply a diagnosis of schizophrenia there?) The diagnosis was changed after "months of observation" to 20 cases of primary behavior disorder, 9 of childhood schizophrenia, and 3 of psychopathic personality. Of the schizophrenics, we are told that "all except two of this group of 11 [9?] had received electric shock treatment before admission to the children's unit. Before admission, the

majority had been described as having shown initial improvement for several months and then as having relapsed or become worse." [96] We are informed that ultimately five were discharged, four as much improved, and were making a good adjustment to the community two years later. Eighteen of the "primary behavior disorders" were improved or much improved after psychotherapy; thirteen were doing very well one to two years later. Of the three patients with "psychopathic personality," one was much improved and one improved; the "much improved" patient was still in the hospital. The discussion, in referring to the previous report,[92] states that it included 10 (30 ?) cases, of which two-thirds made a good adjustment. Apart from the arithmetical inconsistencies in these two papers, they indicate a major dissent from the argument that ECT is of benefit in childhood schizophrenia, and at least imply a marked disagreement with the Bellevue criteria for its diagnosis. It is regrettable that the authors do not supply detailed and accurately reported data, which would be required in order to evaluate these contentions. Lack of proof for the value of ECT is, however, indicated in the last study we shall discuss.

The only study comparable in size to the Bellevue project is that carried out at Hopkins.[94] The population consisted of 80 autistic children who had been known to the clinic for at least four years and who had attained the age of 9 years or more. We were able to trace 63 (79%); the fragmentary data (two to three years) available on the lost cases were in line with the trends in the major group. The median and average age for the children studied was 15 years; the median and average follow-up period, nine years. Outcome was classified into three categories: "good" (patient functioning well academically and socially), "fair" (patient able to attend school at about grade level but distinctly deviant in personality), and "poor" (maladaptive functioning, characterized by apparent feeblemindedness and/or grossly disturbed psychotic behav-

ior). Of the total group of 63, 3 were classified as having a good, 14 a fair, and 46 a poor outcome. Thus, about 27% were functioning at a fair to good social level, a figure remarkable consistent with the Bellevue finding (25%).

On closer examination of the data, however, it became apparent that those children who failed to develop, or, once having developed, lost the ability to communicate by speech did much more poorly than the others. Taking as the line of demarcation the presence of speech with communicative value at the age of 5, we found 32 "speaking" and 31 "nonspeaking" children. Of the former group, 16 (50%) achieved a fair to good adjustment, whereas only 1 (3%) of the latter group did so. (The probability of this difference being due to chance alone is less than 1 in 1000.) Failure to develop speech may be regarded as an index of the severity of the autistic process; it, more than any other feature, seemed to determine outcome. So different is prognosis in the two clinical groups that the thought presents itself that we may be dealing with two syndromes rather than one. Against this is the observation that those originally speaking children with poor outcome were clinically similar to the bulk of the nonspeaking children in final appearance.

The peculiarities so characteristic of the autistic children continued to be apparent as time progressed. In our experience they have not developed in the direction of typical schizophrenic patterns with hallucinations and delusions. Their most salient features are the extreme degree of withdrawal and the obsessive traits. The almost total isolation from human relationships in the most severely autistic group dictates a progressive deterioration of intellectual functioning, so that many are now superficially similar to feebleminded children, though the more specific features usually remain evident to closer examination. The data supplied by this long period of observation tend to support the contention that early infantile autism is "the earliest possible manifestation of childhood schizophrenia." [23]

With respect to the question of possibly effective therapeutic measures, the study "failed to reveal any correlation between formal psychiatric treatment and the clinical outcome." [24] In our experience, ECT, various drugs, and intensive psychotherapy had no predictable effect on course. However, we were struck by the considerable efforts extended by schools and parents on behalf of those children who have improved; we cannot escape the feeling that these efforts were important in their recovery. Certainly, autistic children, if they have any potential for response, are in need of supportive measures which can reinforce their potentialities by creating the conditions for successful interpersonal relationships. We cannot, of course, predict with any certainty what vicissitudes of development the future holds for those children who are now functioning at a better level. Periodic reevaluation alone will supply the answers to the question of their ultimate adjustment in adult life.

Conclusions

At this point in the history of experience with childhood schizophrenia it would appear justified to state that about one-fourth of the cases can be expected to attain a moderately good social adjustment during adolescence, about one-third to deteriorate and require continuous institutionalization, and the remainder to fluctuate about a marginal level. From other considerations, the future prospects of 50%-75% of the total group of these children would appear to be rather poor; if they cannot function adequately under the relatively protected conditions of childhood and adolescence, it seems unlikely that they will survive the more stringent demands imposed by adulthood. These general statements can be made somewhat more definite in the group of autistic children; with adequate language function, about 50% have a chance of reaching a fair to good social outcome; in

its absence, almost none can be expected to achieve this level. There is as yet no evidence that any particular therapeutic agent (including electric shock therapy) can be depended upon to modify outcome of childhood schizophrenia, though the general measures of mental hygiene and "milieu therapy" should be pursued no less avidly in this group than in any other.

The data supplied by this survey of the literature provide a preliminary basis for comparison with claims of therapeutic efficacy. Unless the results of treatment programs indicate appreciably more than 25% of the cases showing substantial improvement, it will be difficult to conclude that the therapy has had a significant effect on outcome.

This review has also served to emphasize the lack of uniformity in criteria for diagnosis. This indicates, at the very least, the importance of specification of criteria in all future clinical reports. I have suggested, on another occasion,[95] that this urgent problem might possibly be in part resolved by organizing meetings at each of the leading centers and inviting key personnel from the other centers to the presentation of cases, considered typical and borderline in the estimation of the host clinic. Perhaps, out of free and full discussion there might emerge an operational definition of the group of childhood schizophrenias. The effort would still be worth while if it succeeded only in acquainting each clinician with the notions his colleagues employ. Until the etiology and pathogenesis of one or more of these syndromes can be scientifically established, such clinical efforts will be crucially necessary if we are to understand each other when we speak of childhood schizophrenia.

Harriet Lane Home for Children (5).

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A Sixteen-Year Follow-Up of Schizophrenic Patients Seen in an Outpatient Clinic

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Introduction

Dementia precox, as described by Kraepelin, was considered in the very great majority of cases to be an illness whose clinical onset was in the second or third decade of life.[1] Kraepelin emphasized that during adolescence the tendency to psychic disease was quite pronounced. Bleuler agreed that in the majority of patients he studied the symptoms became manifest soon after puberty.[2] He thought that age of onset per se, however, had little value in establishing a prognosis. This has seemed to be the over-all finding of the many follow-up studies which have been reported since. Bellak,[3] reviewing the literature, feels that only those onsets prior to puberty or after the age of 40 are of poorer prognostic significance. Some workers, however, such as Rennie,[4] talk of a poor prognosis for patients with onset before 21 years of age. Unfortunately, they lump together adolescents and preadolescents (juvenile schizophrenics), as their age division always extends from 10 through 20 years.

The present study originated from an interest in learning more about what happened clinically to adolescents with such a diagnosis as they grew older. Were they able to function in the community, and, if so, how well? Did they spend most of their lives in mental institutions or at home? There was curiosity as to what extent these episodes were transient developmental crises and to what extent they were the first manifestations of serious illnesses which might handicap the patients for the rest of their lives. To help answer such questions, a follow-up study was done on patients seen in an outpatient clinic for whom the diagnosis of schizophrenia had first been made at the ages of 15 through 21.

Material and Methods

Just over 3000 patients were seen in a community psychiatric outpatient clinic during a seven-year period. Of these, 304 were classified as schizophrenic, 59 of whom were selected for this study. These 59 patients had come to the clinic as adolescents, at which time the diagnosis was initially made. Those whose illness had started at an earlier age, the juvenile schizophrenics, were excluded from the group. The diagnostic criteria used were reviewed. With a few possible exceptions, which will be discussed, they were found to be consistent with Kraepelinian criteria for the diagnosis of dementia precox.

Most of the patients had relatively brief clinic contacts (Table 1): 58%, less than 5 interviews; 35%, 5 to 25 interviews, and 7%, over 25 interviews. The period between the initial clinic visits and the study (1956) ranged from 8 to 24 years, with a mean and median of 16 years. They came referred by the various services of the Grace-New Haven Community Hospital, on the urging of their families or family doctors, from other hospitals, or, less frequently, from Veterans' Administration installations, welfare agencies, school boards, or private psychiatrists.

Of the 59 patients, 54 were successfully located by referring to old clinic records, reviewing the files of the three Connecticut state mental hospitals, and contacting the initial referring agencies, schools, bureaus of missing persons, relatives, and neighbors. It is on these 54 patients, almost all of whom were Connecticut residents, that this study was based. Eighty-three per cent came from the two lower socioeconomic classes (Classes IV and V), as determined by Hollingshead's[6] two-factor index of social position, which divides the population into five classes based on education and occupation. Forty-three were personally interviewed; two had died, two refused to be seen, and seven were out of state, unable to come in for an interview because of psychiatric hospitalization.

The follow-up interviews were all made by the same person. The interviewer, without previously

TABLE 1.—*Data on Fifty-Four Schizophrenic Patients*

Level of Adjustment	No. of Patients			Marital Status			Social Class Standing *					No. of Clinical Visits			Hospitalization	
	Male	Female	Total	Single	Married	Divorced	V	VI	III	II	?	<5	5-25	>25	No. of Pts. Hospitalized	No. of Pts. Not Hospitalized
Good	9	5	14	1	13	..	5	6	1	..	1	6	7	..	8	6
Mediocre	10	4	14	11	3	..	6	4	2	..	2	8	5	1	11	3
Poor { Living at Home	4	9	13	11	1	..	8	3	..	2	..	7	4	2	13	..
Poor { Hospitalized	9	4	13†	10	..	3	7	5	..	..	1	9	2	1	13	..
Totals	32	22	54	33	17	4	26	18	3	2	4	30	18	4	45	9

* Of patient's parents, based on Hollingshead's Index of social position.
† Two died during hospitalizations.

notifying the patient, visited the home and remained for 30 to 60 minutes. If the patient was not in, repeated visits were made until he was contacted, with no explanation given to other members of the family prior to the interview. It was found that this was the most effective approach to reach them. Those hospitalized within Connecticut were personally interviewed on the wards.

The interviewer introduced himself to the patients as a doctor, a psychiatrist, who had come to ask for their help in this way: "The Grace-New Haven Hospital psychiatric outpatient clinic wants to improve its services to the community. To do this, your experiences as a patient would be of help to us." Thereafter the interview followed as closely as possible a predetermined structure. Facts were gathered around their personal history, family history, home situation, degree of community interaction, and work record. They were asked to evaluate how much help they felt they had received from the clinic or from other psychiatric sources. The interviewer recorded his own clinical impressions of the patient, the family, and the response to his visit. In the 11 cases in which direct contacts were not feasible, information was obtained from collateral sources, such as hospital records and family informants.

With such material available, the patients were placed into one of three groups. These were called good adjustment, poor adjustment, and mediocre adjustment. For good adjustment a person had to satisfy certain criteria: a good work record (one job for at least three years) and evidences of active community or social interactions. Furthermore, there could be no visible bizarre symptomatology, and the patient's behavior had to appear relatively integrated and socially adapted. It was recognized that these criteria did not rule out that such a patient might still have definite limitations. Patients in the poor-adjustment category had none of these attributes. A subdivision was made for those actually residing in mental hospitals and

those living at home, yet appearing just as sick. All others came under the heading of mediocre adjustment. These usually had overt neurotic or psychotic symptoms, but functioned intermittently and marginally in the community.

Clinical Findings

The over-all results may be summarized as follows:

Adjustment Group   Per Cent of Sample

Good 26
Mediocre 26
Poor 48

     Hospitalized . . . 24%
     Living at Home . . . 24%

Eighty-three percent of the entire group had one or more periods of psychiatric hospitalization at some time during the follow-up period. The frequency and duration of these periods were greatest in the poor-adjustment category.

Before the follow-up visits were made, the clinical records were read in an attempt to predict how the patients fared. These predictions proved inaccurate, mainly because the interview notes consisted merely of descriptive psychopathology. There was no mention of the patient's assets or of the interpersonal and dynamic forces involved in the presenting illness. No correlation could be made either with the size of the family or with the relative position of the patient among his siblings. The median age of patients when first seen in the clinic was the same in all groups—19 years. What seemed most striking to the investigator was the lack of interest expressed by the resident

psychiatric staff in the clinic records. For example, the patients were repeatedly described as "poor candidates for psychotherapy." It was interesting that the patients expressed almost unanimously the feeling that they had not benefited from their clinic interviews, and many generalized this complaint to all their psychiatric contacts.

It seems appropriate here to mention the subjects' receptiveness to the study. The overwhelming majority were quite eager to talk once their initial suspiciousness had been allayed. They were surprised and gratified that a doctor would come to visit them. Many felt they would not wish to return to the psychiatric clinic to discuss their problems; yet they willingly discussed their problems during the home visit. Those families that were present during the interviews often were less receptive than the patients, and several were overtly hostile.

Good Adjustment—26%.—This group was the only one in which there might have been some questions about the validity of the initial diagnosis. One-third seemed to have been based on isolated criteria, such as flatness of affect, bizarreness of the presenting symptom, and excessive shyness. Possibly some of these might now have been called schizoid characters. The remaining diagnoses were clear-cut.

Half of the patients of this group were described as having had an acute onset of their disease. This meant that the onset could be correlated with some specific event, such as the death of a parent, sibling breakdown, going into the service, or marriage. As there was no historical material available describing the period before the clinical symptoms appeared, the importance of "acuteness of onset" could not be evaluated.

In this good-adjustment group certain facts stood out (Table 1). Almost all of the patients had married. Most of them had been upwardly mobile, moving to a higher social class than that of their parents. Forty-three per cent had no hospitalization. For the remaining patients, the median time of hospitalization was 2.5 months (Table 2). Fifty per cent of these hospitalizations were in private, military, or VA installations. Their clinic contacts were the longest. None had any other outside psychiatric help. In three cases, the clinic staff urged hospitalization, which was refused; yet the patients apparently did quite well.

Two general patterns of social adjustment were noted. Some patients remained with their parents and benefited from mutually supportive and productive relationships with their families. Others limited their activities because of phobic or obsessive symptoms, but nevertheless functioned successfully.

Poor Adjustment—48%.—These patients were severely psychotic. One-half were found on the chronic wards of state hospitals, where they had been eight to nine years.* The others were living at home (Table 2), having been previously hospitalized for three years.† In all instances the disease developed insidiously; there was no acute onset. No patient apparently reached any significant level of maturity. The few that had married were unable to sustain this relationship. With the exception of two patients living at home who received prolonged outpatient therapy, the group had relatively little contact with community psychiatrists (Table 1).

*Median period of time.
†Median period of time.

TABLE 2.—*Range of Years Hospitalized*

Level of Adjustment		Total No. of Pts. Hospitalized	Median Years of Hospitalization	State Institutions		Private Institutions *	
				No. of Pts.	Range, Yr.	No. of Pts.	Range, Yr.
Good		8	0.21	2	0.7–1.8	7	0.1–0.3
Mediocre		11	0.40	8	0.1–1.3	7	0.05–2.3
Poor	At home	13	3.00	13	0.3–11.9	2	0.1–0.5
	Hospitalization	13	8.85	13	1.2–16.5	7	1.01–8.0

* Private, VA, or military.

In each case there appeared to have been initial family interest, which was not necessarily beneficial to the patient. This interest or involvement gradually waned for those who remained hospitalized after they had made repeated unsuccessful visits home. For the rest, each family handled the problem differently, but in all there was a measure of acceptance of the patient. This varied markedly, along with the degree of family supervision or control, which was a function not only of the family's reaction but also of the kind of behavior the patient manifested. Whether the family's reaction and the patient's behavior were related, and whether different clinical courses were really a function of different kinds of schizophrenias were questions which could not be answered in this paper.

In the poor-adjustment category were found the five patients who had been lobotomized. Three lived at home; two were still hospitalized.

Mediocre Adjustment—26%.—This group was the most heterogeneous. Many were hospitalized for relatively brief periods of time (Table 2). Some remained married successfully. Almost all of them were living with their parents and had only their work as outside interest. One tried to devote himself to religion. Two had very complex obsessive systems, for which they were receiving some psychiatric help. One woman looked after her three children and her home, but in such a chaotic fashion that it was hard to see just how she managed. These patients were functioning in society, but not very securely or very effectively.

Comment

Of the patients followed, one-quarter made a good adjustment. These had fewer and briefer hospitalizations, as well as relatively acute onsets of disease. In most cases there was no obvious relation between improvement and psychiatric interaction. For most patients, including the other three-quarters, who remained handicapped throughout their lives, psychiatrists did relatively little. They did not seem to enjoy working with them, nor did the patients feel they had benefited from the contact.‡

It is difficult to compare these results with similar follow-up studies because of the variability of the criteria. Other studies included patients of all ages, most of them being in their 20's and early 30's. The follow-up periods varied from 6 months to 20 years. Large numbers of patients were evaluated without any personal interviews. The criteria for improvement or recovery were not consistent. In spite of this confusion, Bellak[3] quotes over-all "improvement" rates varying from 22% to 54%, with the majority clustering about 40%. With such standards, possibly the mediocre-adjustment group should be included in this study, to give an over-all "improvement" rate of 52%.

Summary

A 16-year follow-up study was done on 54 adolescent schizophrenics seen in a community psychiatric outpatient clinic. The validity of the diagnoses and the methods of locating and then interviewing the patients are discussed. The results are tabulated in terms of three levels of patient adjustment— good, mediocre, and poor. Patients were categorized on the basis of their history, work record, community and family interactions, and the clinical impressions of the interviewer. Comparative data were given for the three groups, such as relative periods of hospitalization, nature of onset of disease, and marital status. One-quarter of the patients were found to have made a good adjustment in life. The others remained severely handicapped. The minimal degree of interaction between patients and psychiatrists was emphasized.

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‡This lack of therapeutic interaction was not further investigated in this paper. Social and cultural factors, as suggested by Robinson, Redlich, and Myers,[8] undoubtedly were important.

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Drug and Milieu Effects with Chronic Schizophrenics

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Introduction

It has long been known in therapeutics that the prescription of several medicinal substances is often more effective than giving one alone. Many substances are known to act as adjuvants or as potentiators of active agents, or they may tend to counteract undesirable side-effects. There immediately comes to mind the use of acetophenetidin (Phenacetin) and caffeine along with acetylsalicylic acid (aspirin), and dextroamphetamine sulfate U. S. P. with amobarbital, as well as any number of newer proprietary preparations which combine the effects of two or more drugs.

When the action of a drug on a given type of patient is well known, it may be meaningfully combined with an equally well-known agent, and the contribution of each may be clinically differentiable. Relatively unknown agents may also be given in combination, in the hope that their combined effectiveness will be greater than that of either drug given singly. In this latter instance, of course, it is much more difficult, if not impossible, for the clinician to determine just what has been the specific contribution of each agent, or how much additional efficacy, or potentiation, has been gained by giving the drugs simultaneously.

Experimentally it is possible, however, by giving various combinations of drugs to appropriately selected groups of patients, to determine rigorously how much is gained by adding each new agent to a "battery" of drugs. In the present investigation four drugs were selected for study in the treatment of catatonic schizophrenics. These drugs were selected on a rational basis, and the experiment was so designed that the effectiveness of the drugs could be evaluated not only singly, but in all of their various combinations.

Rationale for Selection of Drugs

1. A Tranquilizer.—It was decided to use reserpine as the basic drug in the experimental battery. This drug is well documented both generally and with specific regard to schizophrenia,[1-3] in which it is said to have a "cathartic" effect.[4] Because this drug is widely used and its relative effectiveness is well known, it is of interest and of immense practical value to determine whether its action may be potentiated and its undesirable features eliminated by concurrent administration of appropriate ancillary agents.

Specifically, it is clinically desirable to eliminate the soporific effects of reserpine without producing agitation or exacerbation of symptoms; it is equally desirable to eliminate the Parkinsonism-like syndrome which frequently results from prolonged administration of high doses of the tranquilizer.

2. An Analeptic.—There have been a number of reports in the literature describing the use of methylphenidate hydrochloride as an analeptic to counteract reserpine—induced drowsiness, retardation, or depression.[5,6] Although probably not effective in itself with chronic schizophrenics, the drug should be further investigated to determine the possible therapeutic gain to be derived from prescribing reserpine in combination with methylphenidate hydrochloride.

3. An Antispasmodic.—A dramatic side-effect of certain ataractics is a Parkinsonism-like syndrome. The appearance of this syndrome is undesirable not only in itself but also because it often results in the

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discontinuance or reduction in dose of the tranquilizer before the patient has received its full therapeutic effect. As an alternative to drug reduction or discontinuance, an antispasmodic may be prescribed. Our drug of choice to counteract this side-effect was trihexyphenidyl, which is a clinically effective agent against Parkinsonism-like side-effects.

4. An Antihallucinogen.—Hallucinations produced through the use of mescaline, *d*-LSD-25, etc., may be counteracted in varying degrees by the tranquilizers methamphetamine and amobarbital.[7] A tranquilizer is already included in our battery. Since the analeptic action of methylphenidate hydrochloride is similar to that of methamphetamine, both agents were not included. On the other hand, it is known clinically that intravenous amobarbital sodium often produces dramatic, though temporary, remission in catatonic states. Although sleep or sedation therapy in general and oral amobarbital in particular are not considered specifics in the treatment of catatonic schizophrenics, it was thought that the role of amobarbital in conjunction with other drugs in the battery deserved investigation.

Subjects

In a previous publication[8] we have described the selection of a group of 48 female chronic catatonic schizophrenics, homogeneous as to age, color, duration of illness, physical condition, and prognosis. These patients were studied on a research ward for a period of 28 weeks (Phase I) prior to the administration of drugs. The patients were evaluated on specially designed rating scales, and during the 28-week period it was found that 39 patients showed measurable improvement, 6 remained unchanged, and 3 were worse.

On the basis of their "change scores," the 48 patients were divided into three groups: those showing the greatest improvement (I), those showing an intermediate amount of improvement (II), and those showing little or no change, or actually getting worse (III). The patients were then redivided into 16 groups of three patients each, consisting of one patient from each of Groups I, II, and III. The individual patients for each group of three were so selected that when their "change scores" were algebraically summated, the totals

were approximately equal for all of the 16 groups. For example, three patients with respective net change scores of -5, -2, and 0 were grouped to form one of the 16 experimental drug groups, approximately equal by algebraic summation to each of the other 15 groups.

The result of this procedure was the designation of 16 groups, all of which were equated not only on the original criteria of age, color, duration of illness, physical condition, and prognosis, but also on the basis of their response to the psychological and sociological influences attendant on a change in milieu. All of the 16 groups, then, had equal likelihood of improvement. Accordingly, we were then in a position to state that any significant differences in improvement among the groups could be related to the administration of whatever drugs the patients were receiving, although not necessarily entirely to the drugs themselves.

Design of Experiment

Statistical Design.—The four drugs which had been selected for study were designated A (reserpine), B (methylphenidate hydrochloride),* C (trihexyphenidyl), and D (amobarbital). These four drugs and their inert placebos were combined in 16 ways, in accordance with the principles of factorial design, as shown in Table 1. The 16 drug groups were assigned to the 16 patient groups by the simple expedient of drawing numbers out of a hat.

TABLE 1.—*Combinations of Reserpine (A), Methylphenidate Hydrochloride (B), Trihexyphenidyl (C), and Amobarbital (D) Used in This Investigation* *

1. ABCD	5. aBCD	9. AbCd	13. aBcd
2. ABCd	6. ABcd	10. aBcD	14. abCd
3. ABcD	7. AbcD	11. aBCd	15. abcD
4. AbCD	8. abCD	12. ABcd	16. abcd

* Upper case letters refer to active agents; lower case, to inert placebos.

Since there were 48 patients and 16 drug groups, it would appear that only 3 patients were selected to receive each drug or combination of drugs. Reference to Table 1, however, reveals that actually eight groups, or 24 patients, received drug A. The same is true for drugs B, C, and D, respectively. The effects of the other drugs are evenly distributed among the seven groups in which the individual drug is not the only one administered. For example, drug B is the only active agent in Group 13. Its effects are combined with that of A in Group 6, of C in Group 11, and of D in Group

10; in Group 2 it is combined with both A and C, and so forth. Similarly, while 12 patients receive each combination of two drugs, 6 receive each combination of three drugs, and only one group receives all four combined drugs. It should be pointed out that additional information about higher-order interactions may be extracted from the data through use of analysis of variance. This design, moreover, makes it possible to retest the drug interactions within the same population with any combination of two, three, or four drugs. This was actually done in Phase III of the investigation (to be reported at a later date).

Despite the current popularity of the so-called "double-blind" technique, this was not employed, for the following reasons:

1. No psychiatrist who is accustomed to the use of tranquilizing drugs in high dosage can long remain unaware, either consciously or preconsciously, as to which patients are receiving the ataractic and which the placebo.

2. The present experimental design obviates the need for the experimenter to conceal from himself "who is getting what." The main, if not the only, reason for keeping the assignment of the drugs a secret from the investigator (or from his ward administrator) is to prevent him from treating preferentially either the experimental or the control group, both in his dealings with them and in his estimate of their improvement. In our present experimental design, with 16 separate groups, there was no unique "experimental" or "control" group; each group was "experimental" in itself, while serving as a "control" for the others. Further, the extreme complexity of the design, and the fact that the patients lived together under outwardly identical circumstances, would have made it extremely difficult for us to influence the course of the experiment had we wished to do so. For example, had we wished to make the combination B and D "look good," we would have had to seek out and treat favorably the patients in Groups 1, 3, 5, and 10, meanwhile exerting great caution not to permit Groups 2, 4, 6, 7, 8, 11, 13, and 15 to do too much better than Groups 9, 12, 14, and 16.

3. Finally, we considered it necessary to have available a list of the distribution of drugs among patients to which we might refer when necessary to adjust dosage. This was especially important with respect to side-effects, since some of our patients received as many as four different agents.

Plan of Drug Administration.—By the beginning of Phase II all patients had become accustomed to taking "something by mouth," in the form of vitamins, iron tablets, etc. Accordingly, it was possible to start all patients, without exception, on oral medication. The initial doses were fairly small.

	Dose, Mg/Day
Reserpine	3.0
Methylphenidate HCl	15.0
Trihexyphenidyl	2.0
Amobarbital	300.0

These were gradually increased to the maximums indicated in the following, all in divided doses:

	Dose, Mg/Day
Reserpine	24.0
Methylphenidate HCl	90.0
Trihexyphenidyl	10.0
Amobarbital	600.0

Records were kept of all undesirable side-effects, which were treated symptomatically or by reduction or cessation of drugs.

Except for us, no one was aware of the identity of the drugs, which were referred to as A, B, C, and D.

Use of Rating Scales.—The same rating scales that were utilized in Phase I, as described in our previous communication, were employed in Phase II. As was our practice during Phase I, ratings of us and by the staff nurse. Patients were seen twice a week, and final ratings were made after were derived from the pooled evaluations by both the drugs had been administered for 16 weeks.

Sources of Error.—1. Time of Year: Phase I began during the summer of 1955 and ran through February, 1956. Accordingly, the drug phase began in the winter and continued into the spring of 1956. We do not know what effect the coming of spring had on our patient population, or in what way this effect may have interacted with the drugs they received.

2. Changes in the Therapeutic Setting: Phase I of the experiment lasted seven months. During this time none of the experimental drugs were given, although ward personnel knew that a "drug experiment" was in progress. Probably the introduction of drugs was welcomed, particularly by nurses and attendants, but also by us. This might be expected to have improved the spirits of significant persons in the therapeutic milieu, and hence may have tended to have a beneficial effect on the patients. This would tend to increase spuriously the significance of change attributable to drugs but should not be reflected discriminately in patients receiving any particular drug or drug combination.

3. Variability of Response to Drugs: It is well known that any given drug may produce a variety of effects in a group of patients and in a single patient over a period of time. This possible source of error was avoided satisfactorily, we believe, by composing our drug groups of persons with varied expectancies of improvement, and also through the use of factorial design, which distributed the effects of a drug over various subgroups and placed it in combination with all the other drugs used in the experiment.

TABLE 2.—*Ratings and Change Scores During the Predrug (Phase I) and Drug (Phase II) Periods* *

Drugs	Phase I			Phase II	
	Initial Rating	Final Rating	Change	Final Rating	Change
ABCD	10	7	−3	10	+3
	15	14	−1	13	−1
	14	11	−3	11	0
ABCd	16	13	−3	9	−4
	16	13	−3	13	0
	16	15	−1	16	+1
ABcD	14	12	−2	10	−2
	17	14	−3	15	+1
	15	14	−1	13	−1
AbCD	15	11	−4	10	−1
	13	12	−1	15	+3
	16	14	−2	13	−1
aBCD	14	9	−5	12	+3
	16	16	0	15	−1
	16	14	−2	14	0
ABcd	17	14	−3	11	−2
	17	14	−3	16	+1
	15	14	−1	14	0
AbcD	16	9	−7	11	+2
	15	16	+1	15	−1
	17	15	−2	15	0
abCD	17	17	0	17	0
	17	15	−2	15	0
	17	11	−6	13	+2
AbCd	17	17	0	17	0
	16	13	−3	10	−3
	17	15	−2	13	−2
aBcD	12	16	+4	17	+1
	17	16	−1	10	−6
	16	6	−10	3	−3
aBCd	17	17	0	13	−4
	17	15	−2	16	+1
	16	10	−6	16	+6
Abcd	12	1	−11	2	+1
	17	17	0	11	−6
	10	14	+4	3	−11
aBcd	15	13	−2	12	−1
	14	10	−4	12	+2
	17	15	−2	14	−1
abCd	15	10	−5	11	+1
	17	16	−1	16	0
	16	14	−2	14	0
abcD	11	11	0	12	+1
	10	8	−2	7	−1
	8	4	−4	8	+4
abcd	17	15	−2	13	−2
	17	13	−4	15	+2
	14	13	−1	13	0

* Upper-case letters refer to active agents; lower-case letters, to inert placebos.

4. "Spontaneous" Fluctuations in Patients' Hospital Course: While it is true that patients had a seven-month period in which to display their propensity for change prior to the phase of drug administration, it is true that, by definition, "spontaneous" changes may occur at any time. An only slightly different question concerns whether or not there is any periodicity or rhythmicity to the clinical status of female chronic catatonic schizophrenics, and whether or not such intrinsic variability might in itself account for the observed changes. There is very little information available on this subject, to which we will have occasion to refer in the final section of this paper.

Results

In Table 2 are presented the ratings and change scores characterizing each patient during both the predrug and the drug phase. In order to determine whether or not there was any systematic influence on changes in patients' clinical status attributable to any drug or combination of drugs, these data were subjected to analysis of variance.† Variance was considered to derive from five sources: from each of the four drugs and from the patients' varying responsiveness to milieu effect, as was evidenced by the distribution of the changes which occurred during Phase I. Since the assignment of patients to a particular drug group was determined by this responsiveness, it could not be ignored in carrying out the statistical analysis. Patients were thought of as demonstrating change during Phase I on each of three levels, one of which was represented by each patient, as described in the section on "subjects," and which as a source of variance is symbolized as L. The drugs continue to be symbolized by A, B, C, and D. Using this notation it was found that one quadruple interaction (ABDL) and two triple interactions (ACL and BCL) were found significant at the 0.05 level of confidence. One main effect, that attributable to L, was found significant at the 0.025 level of confidence.

Accordingly, changes demonstrated by patients during Phase II may be said not to be attributable to any drug or drug combination, but seem best to be predicted in terms of the amount of change which the patients demonstrated during the predrug phase. A product-moment correlation was computed relating the changes occurring during Phase I and those occurring during Phase II, and an r was obtained of -0.40. This finding indicates that there is a tendency for patients improving during Phase I to get worse during Phase II, and vice versa, regardless of the drug received. This tendancy is of high statistical significance.

Because it seemed that we were dealing not with a simple inverse relationship, but, rather, with a curvilinear one, this relation

†Mrs. Lila Galanter made a significant contribution to the statistical analysis of the data.

was investigated statistically and was found to be the case. The correlation ratio, η, was therefore computed and was found to be 0.61, which is also highly significant in a statistical sense.

Comment

There can be little doubt that insofar as drugs are concerned this paper reports only negative findings. In our group of 48 white female chronic catatonic schizophrenics, no significant effect on the clinical status was noted with reserpine, methylphenidate hydrochloride, trihexyphenidyl, or amobarbital, or with any combination thereof, administered over a period of 16 weeks. This was true whether the apparent drug effects were compared with each other, with the initial ratings, or with the predrug phase. As described in our previous communication, patients did change during the course of this investigation; this change we termed "milieu effect." No significant addition to this effect was made by drugs.

One conclusion seems inescapable: The setting up of fairly elaborate projects for the testing of drugs does seem to benefit patients clinically (although this investigation was not designed to test that hypothesis).

It is striking that there should be an inverse ratio between improvement during the predrug and improvement during the drug phase of this investigation. This raises an interesting question for future investigation: Will patients who benefit from milieu changes continue to benefit if the milieu is consistently modified rather than drugs being introduced in the hope that the patient will thus be "made just a little better" or "carried over the hump." Further, should drugs be reserved for those patients who fail to respond otherwise to administrative or psychotherapeutic measures, as contrasted with the policy of giving drugs routinely to all newly admitted patients on the basis of their diagnosis or degree of manifest disturbance? What is suggested for investigation is obviously a

"trial in milieu" of each patient before prescription of therapy.

Sabshin and Ramot[9] have commented that enthusiasm on the part of hospital personnel seems to result in more positive drug effects. It may be that our negative results reflect a negative attitude on our part. If this is the case, the attitude was an unconscious one; we had hoped that our investigation would be objective, and hence impartial. It is true that objectivity and impartiality are not equivalent to enthusiasm, and we must acknowledge that we began this study with no overwhelming enthusiasm for the drugs to be employed. We were, however, enthusiastic about our project, which, accordingly, we feel had an over-all therapeutic value. There are many dynamic reasons that this should be the case, but we do not feel that discussion of them is warranted at this time.

Summary

Four drugs, reserpine, methylphenidate hydrochloride, trihexyphenidyl, and amobarbital, in 16 combinations, were administered in large doses to a selected group of 48 white female chronic catatonic schizophrenics, who have been studied over a period of seven months. Changes occurring in the drug phase of the experiment are compared with changes, termed "milieu effect," occurring during the predrug phase. Extensive statistical analysis reveals that no drug or combination of drugs studied contributes significantly to changes in the patients' clinical status, and it is found that changes occurring during the drug phase of the investigation are best predicted from changes occurring during the predrug phase. This relationship is curvilinear but tends to be inverse: Patients improving during the predrug phase tend to do poorly on drugs and vice versa. The question is raised as to the possible significance of "trial in milieu."

Our negative results, insofar as drugs are concerned, are discussed in relation to our enthusiasm for research and impartiality re-

garding the value of drugs with chronic hospital patients.

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Adrenal Cortical Function in Anxious Human Subjects

Effect of Corticotropin (ACTH) on Plasma Hydrocortisone Level and Urinary Hydroxycorticoid Excretion

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Evidence has been presented in a previous communication from this Institute that in anxious subjects the plasma level of hydrocortisone and the urinary excretion of one group of its metabolites, the hydroxycorticoids, are almost double the values found in normal persons.[1] The elevation in these levels may be explained by one of two alternative hypotheses: an increased rate of production of hydrocortisone by the adrenal cortex or a diminished rate of disposal of the hormone. The rate of disappearance of hydrocortisone from plasma has been shown to be significantly faster in anxious patients than in normal subjects, and, furthermore, the anxious subject metabolized hydrocortisone in such a fashion as to produce a smaller proportion of hydroxycorticoids than the normal control subject.[2] It is therefore likely that the high endogenous levels of plasma hydrocortisone and urinary hydroxycorticoids found in anxious patients are due to an increased rate of production of hydrocortisone coupled with an increased rate of disposal of the hormone. The present paper is a report of a study in which the rate of production of hydrocortisone, as reflected by the plasma hydrocortisone level and the urinary excretion of hydroxycorticoids, was determined for anxious and normal subjects following the intravenous administration of corticotropin (ACTH).

Subjects and Methods

The subjects of this study were patients who were overtly anxious and were capable of reporting their feelings to an observer or were anxiety-prone patients whose histories revealed previous experiences of anxiety provoked by various life situations. These subjects have been described more fully elsewhere.[1-3] The patients were divided into two groups, each receiving corticotropin by a different method of administration.

The first group of patients consisted of seven men and six women, whose mean age was 37 years. A 24-hour urine sample was collected from each subject on a preexperimental day for the determination of endogenous hydroxycorticoid output.

On the experimental day, each subject voided; a blood sample was drawn for the determination of endogenous plasma hydrocortisone, and an intravenous infusion of 15 U.S.P. units of corticotropin in 500 cc. of 5% dextrose in water was started and permitted to continue for four hours. Blood samples were drawn one-half, one, two, and four hours after the initiation of the infusion for the determination of hydrocortisone. After the conclusion of the infusion, another urine sample was obtained for the determination of hydroxycorticoids.

The second group of anxious subjects (one man and four women) averaged the same age. They received an intravenous infusion on each of four consecutive days: 5% dextrose in water on the first day; 5 units of corticotropin in 5% dextrose on the second day; 10 units of corticotropin in 5% dextrose on the third day, and 15 units of corticotropin in 5% dextrose on the fourth day. The first day was intended to familiarize the subjects with the intravenous procedures and to establish

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TABLE 1.—*Plasma Hydrocortisone Levels of Anxious and Normal Subjects Before and After Receiving 15 Units of Corticotropin Intravenously over Four Hours*

Group	No. of Subjects	Plasma Hydrocortisone Level, γ/100 Ml.*				
		0	½ Hr.	1 Hr.	2 Hr.	4 Hr.
Normal	13	13.8±2.7	23.2±6.7	30.9±8.2	36.1± 8.6	36.6± 8.5
Anxious	13	18.0±2.2	30.0±6.7	39.1±7.3	42.6±10.5	41.2±13.9
t		3.61	2.60	2.72	1.71	1.02
P		<0.01	<0.02	<0.02	Not sig.	Not sig.

* Mean±standard deviation.

prexperimental levels of plasma hydrocortisone and urinary hydroxycorticoids. On the three experimental days the infusion lasted for three hours, during which 375 cc. of fluid was administered. The rate of administration was identical with that for the first group, but only three hours of infusion was given, since the subjects in the first group exhibited a maximal elevation of plasma hydrocortisone within three hours.

A three-day tolerance test was employed in order to determine whether repetitive stimulation with increasing doses would differentiate anxious from normal subjects to a greater degree than a single tolerance test. On each day of testing blood samples were drawn immediately before, two hours and two and one-half hours after the start of the infusion, and two hours after its termination. A 24-hour urine sample was collected from each subject on every testing day.

Two groups of subjects served as normal controls for this study. One consisted of five male and eight female hospital employees, with an average age of 35 years, who were treated exactly as the first group of anxious subjects. A second group of normal controls consisted of five male soldiers who received the same treatment as the second group of anxious subjects. All of the control subjects lived at home or in their barracks and were entrusted with the collection of their urine samples.

All of the subjects received Wilson's Corticotropin Solution; the first group of anxious and normal subjects received Lot No. 90664 and the second, Lot No. 95116.

The patients and control subjects were in good physical health, as determined by careful physical examination. The psychiatric status of the patients and the soldier controls was determined by means of a diagnostic interview. The patient group manifested anxiety levels considerably higher than those in the control group. Several patients had been receiving tranquilizing drugs in small quantities for some time, which after a preliminary dose do not increase corticotropin production and do not interfere with the Porter-Silber reaction, which is the basis of the chemical methods employed. No medication was received by any subject for the 12-hour period preceding the beginning of the intravenous infusion.

The level of plasma hydrocortisone was determined by the method of Nelson and Samuels.[4,5] Urinary hydroxycorticoids were determined by the method of Reddy,[6] as modified by Brown.[7] All urine samples were checked for accuracy of collection by means of a creatinine determination.[8]

Results

Response to Single Dose of Corticotropin.

The hydrocortisone levels in the plasma of anxious and normal subjects before and after receiving 15 U. S. P. units of corticotropin for four hours are given in Table 1. The preexperimental level of hydrocortisone in the anxious subjects was significantly greater than that in normal subjects, as we have previously reported.[1] Following the administration of corticotropin, the hydrocortisone level of the plasma of the anxious patient was greater on every sampling occasion, but the increase in level was not significantly different (Table 2).

The excretion of urinary hydroxycorticoids during a four-hour morning period

TABLE 2.—*Change in Plasma Hydrocortisone Level in Anxious and Normal Subjects Following Administration of 15 Units of Corticotropin Intravenously over Four Hours*

Group	No. of Subjects	Change in Plasma Hydrocortisone Level, γ/100 Ml.*			
		½-0	1-0	2-0	4-0
Normal	13	9.41±7.39	17.05±9.61	22.30± 8.40	22.81± 7.46
Anxious	13	12.02±6.05	21.11±5.95	24.56±12.80	23.22±15.08
t		0.98	1.27	0.53	0.09
P		Not sig.	Not sig.	Not sig.	Not sig.

* Mean±standard deviation.

TABLE 3.—*Excretion of Urinary Hydroxycorticoids by Anxious and Normal Subjects Before and During Administration of 15 Units of Corticotropin Intravenously over Four Hours*

Group	No. of Subjects	Urinary Hydroxycorticoid Excretion, γ/Min.* †		
		Before ACTH	During ACTH	Increase
Normal	13	8.23±4.68	13.88±4.95	5.64±3.96
Anxious	9 ‡	9.52±4.97	18.74±7.81	9.19±7.02
t		0.61	1.65	1.34
P		Not sig.	<0.10	<0.10

* For the period 8:30 a.m. to 12:30 p.m.
† Mean±standard deviation.
‡ Complete data for only nine subjects.

was not significantly different in anxious and in normal subjects, as shown previously.[1] However, after the administration of 15 units of corticotropin there was a greater hydroxycorticoid output by the anxious patients for a comparable four-hour period (Table 3). The increase in hydroxycorticoid output following the corticotropin infusion was 60% greater in the anxious patient group, despite the fact that there was no similar increment in the plasma hydrocortisone level for the same time span. In view of the findings on the disappearance of hydrocortisone from plasma and its metabolic fate,[2] this result can only represent an increase in the production of hydrocortisone by the anxious patient group.

Response to Three Consecutive Doses of Corticotropin.—With the idea that the differences between anxious and normal subjects might be accentuated by repetitive stimulation of the adrenal cortex ("priming"), a small group of anxious and normal subjects were given intravenous infusions of corticotropin on three consecutive days, as previously described. The plasma hydrocortisone level of the normal subjects on their first occasion of testing was greater than that of the anxious subjects, a finding opposite that reported previously.[1] This was chiefly due to the small size of the normal group, since one subject accounted for most of the elevation. The normal value of the anxious subjects may also be due to small sample size. Numerous other studies have consistently indicated an elevation in level for such patients. The present group of subjects were selected by the same criteria that were employed previously. The plasma hydrocortisone levels of the anxious patients were not significantly greater than those of the normal controls following corticotropin administration on any of the sampling occasions (Table 4). The precorticotropin levels of hydrocortisone on each testing day were not increased in the normal group, as shown by an analysis of variance, while the anxious subjects did manifest such a progressive increase (normals: $F=1.14$, P not significant; anxious patients: $F=4.00$, $P<5\%$). The initial level increased 78% over the four testing days in the anxious group, while it dropped 11% in the normal group for the comparable period.

Although the anxious group experienced a priming effect in that the previous day's treatment influenced the subsequent morning's level, the change in level of hydrocortisone on each day of testing was not significantly different in the two groups (Table 5).

On the assumption that a priming effect might be exerted by a prolongation of the

TABLE 4.—*Plasma Hydrocortisone Levels of Anxious and Normal Subjects Before and After Receiving Corticotropin Intravenously on Four Consecutive Days*

Group	No. of Subjects	Plasma Hydrocortisone Level, γ/100 Ml.*															
		No ACTH				5 U.S.P. Units ACTH				10 U.S.P. Units ACTH				15 U.S.P. Units ACTH			
		0	2 Hr.	2½ Hr.	5 Hr.†	0	2 Hr.	2½ Hr.	5 Hr.†	0	2 Hr.	2½ Hr.	5 Hr.†	0	2 Hr.	2½ Hr.	5 Hr.†
Normal	5	17.5±5.6	..	27.8±7.2	13.8±6.5	22.1±9.4	41.6±3.6	39.8±13.5	32.7±6.3	16.0±7.8	33.9±10.6	35.5±7.1	34.9±10.1	15.5±6.4	23.0±18.2	52.0±13.2	51.5±9.7
Anxious	5	12.2±2.9	..	16.9±6.7	19.2±6.0	15.3±4.9	28.9±7.9	34.6±6.3	32.6±10.6	17.8±6.2	44.1±12.6	40.7±5.2	41.6±12.9	21.7±4.4	40.1±8.9	46.8±6.5	46.1±11.0
t		1.90	..	2.48	1.37	1.43	3.30	0.86	0.01	0.42	1.36	1.33	0.91	1.80	0.79	0.88	0.82
P		<0.10	..	<0.05	Not sig.	Not sig.	<0.05	Not sig.	Not sig.	Not sig.	Not sig.	Not sig.	Not sig.	Not sig.	Not sig.	Not sig.	Not sig.

* Mean±standard deviation.
† Five hours after the start of the corticotropin infusion or two hours after its termination.

TABLE 5.—*Change in Plasma Hydrocortisone Level in Normal and Anxious Subjects Following Administration of Corticotropin Intravenously on Four Consecutive Days*

Grp.	No. of Subjects	Change in Plasma Hydrocortisone Level, γ/100 Ml.*														
		No ACTH			5 U.S.P. Units ACTH				10 U.S.P. Units ACTH				15 U.S.P. Units ACTH			
		2½-0	5-0	5-2½	2-0	2½-0	5-0	5-2½	2-0	2½-0	5-0	5-2½	2-0	2½-0	5-0	5-2½
Normal	5	10.22± 10.50	-3.76± 10.51	-13.98± 5.19	19.56± 7.30	17.68± 15.85	10.60± 10.49	-7.08± 9.78	17.94± 11.83	19.48± 13.05	18.94± 13.22	-0.54± 15.17	17.48± 20.27	36.52± 13.91	35.98± 10.61	-0.54± 4.26
Anxious	5	4.58± 2.92	6.98± 7.48	2.30± 3.09	13.56± 9.19	19.32± 7.68	17.30± 19.17	-2.02± 19.18	26.26± 16.23	22.86± 8.20	23.26± 12.89	0.90± 15.74	18.40± 8.20	24.50± 8.30	24.40± 7.96	-0.10± 7.05
t		0.90	1.86	6.03	1.14	0.21	0.69	0.53	0.93	0.49	0.58	0.15	0.09	1.66	1.95	0.12
P		Not sig.	<0.10	<0.001	Not sig.	Not sig.	Not sig.	Not sig.	Not sig.	Not sig.	Not sig.	Not sig.	Not sig.	Not sig.	<0.10	Not sig.

* Mean±standard deviation.

action of corticotropin on the adrenal cortex, the plasma hydrocortisone levels were determined after the termination of the intravenous infusion. Two hours after stopping the infusion (five hours after its beginning), the level of hydrocortisone in the plasma was not significantly greater in the anxious group of subjects. Likewise, the change in level from the start of the infusion (5-0) or from the end of the infusion (5-2½) was not greater in the anxious group.

the increase is almost three times as great in the triple tolerance test as in the single one, although the same dose was employed, indicates a large priming effect.

The change in hydrocortisone level in the plasma following the administration of several doses of corticotropin to the subjects of both groups provides an assay for corticotropin according to the method of Persky and Heath.[6] Comparison of the two log dose-response lines by the standard pro-

TABLE 6.—*Excretion of Urinary Hydroxycorticoids by Anxious and Normal Subjects Receiving Progressively Increasing Doses of Corticotropin over Four Days*

Group	No. of Subjects	Urinary Hydroxycorticoid Excretion, Mg/Day*						
		No ACTH	5 U.S.P. Units ACTH	10 U.S.P. Units ACTH	15 U.S.P. Units ACTH	5-0	10-0	15-0
Normal	5	4.69±3.01	10.09±4.76	11.66±5.91	10.97± 5.55	5.40±3.20	6.97±3.34	6.27±3.90
Anxious	5	3.73±4.93	12.45±6.99	13.51±6.50	19.57±10.51	8.72±4.27	9.79±2.75	15.84±7.24
t		0.43	0.63	0.47	1.60	1.39	1.46	2.60
P		Not sig.	Not sig.	Not sig.	0.10	0.10	<0.10	<0.025

* Mean±standard deviation.

On each of the days during which corticotropin was administered, the anxious subjects excreted greater amounts of hydroxycorticoids than the control subjects (Table 6). The increment of hydroxycorticoid output above the endogenous level was greater at each dose level for the anxious group, achieving a high degree of significance when 15 units was infused. The difference in increment was progressive, for the excretion of hydroxycorticoids in the anxious group was 62% greater than that in the control group after 5 units and 153% greater after 15 units. As in the case of the single corticotropin dose, this increase represents a real increase in the production of the adrenal cortical hormone. The fact that

cedures [10] gave ambiguous results (Table 7). Although the two groups differed significantly as shown by their variance ratio, the difference between their slopes and their intercepts on the Y-axis did not achieve significance despite a large difference in

TABLE 7.—*Comparison of the Log Dose-Response Lines Obtained for Anxious and Normal Subjects* *

Group	Standard Deviation About Line (σ_{yx})	Slope of Line (b)	Intercept of Line on Y-Axis (a)
Normal	14.65	35.88	-9.83
Anxious	6.54	10.96	11.72
F	5.02		
t		1.19 †	0.11 ‡
P	0.01	Not sig.	Not sig.

* Response at two and one-half hours.
† Based on the assumption of a difference in variance.
‡ Based on the assumption of no difference in slope.

the values of their slopes and intercepts. This lack of significance is primarily due to the small sample population in each group. The data suggest that the anxious subjects respond to progressively increasing doses of corticotropin with a smaller response increment than do the normal controls.

Comment

In the present study anxious patients as compared with normal controls responded to the stimulus of corticotropin with little increase in level of hydrocortisone in the plasma but with a large increase in urinary output of hydroxycorticoids. This may result from an increased production of hydrocortisone by the adrenal cortex with no change in the proportion of urinary metabolites excreted as hydroxycorticoids, or to an increase in the rate of conversion of hydrocortisone to hydroxycorticoid-like compounds (dihydroxyacetone side-chain) without an increase in adrenocortical activity. However, anxious patients actually convert hydrocortisone to hydroxycorticoids to a slighter degree than normal subjects after a test load of hydrocortisone.[2] The conclusion remains that anxious patients produce hydrocortisone at a considerably greater rate than normal controls. The failure of this increased productivity to be manifested as a rise in the plasma hydrocortisone level is due to the fact that anxious patients remove hydrocortisone from plasma faster than normals. After repetitive stimulation with corticotropin (endogenous or intravenous), the rate of production mounts to such a degree that the removal mechanism is unable to maintain a steady plasma level and the level rises until a new steady state is achieved.

The quantity of hydrocortisone produced by anxious subjects was not directly obtained in the present study. A crude approximation based on the urinary hydroxycorticoid output following repetitive corticotropin stimulation and on the proportion of hydrocortisone excreted as hydroxycorticoids[2] suggests that the anxious patient

produces about four times the normal rate, or about 100 mg. per day. Recently, Peterson and Wyngaarden showed that normal subjects stimulated maximally with corticotropin produced 130-150 mg. per day.[11] This finding suggests that the anxious patient is close to the maximum possible adrenal cortical secretion—a result which we had anticipated in a previous study.[1] A direct assessment of adrenal cortical hormone production in anxious subjects, employing hydrocortisone-4-C^{14}, will be reported shortly in another paper.

The increased activity of the adrenal cortex in the anxious patient may be due to a prolonged action of circulating pituitary adrenocorticotropic hormone (ACTH) or to an increase in ACTH production and discharge into the circulation. The finding that the plasma hydrocortisone level was not significantly different in the anxious and the normal subjects two hours after termination of the corticotropin infusion is not consistent with the former hypothesis. Although the second view was not directly tested, acute stresses have been shown to increase circulating ACTH levels enormously.[12] Furthermore, the log dose-response curve for the anxious patients obtained in the present study was almost flat. This finding may be due to the fact that the anxious patient's ACTH level was so great that the log dose-response test was conducted in an ACTH range where the relationship was not linear. Final decision as to the mechanism of increased adrenocortical secretion in anxious patients must await direct measurement of the level of ACTH in blood.

Although the anxious patient produces increased amounts of hydrocortisone, he also removes this substance from the circulation faster and consequently does not exhibit the symptomatology of the subject with adrenal hyperplasia. It is not presently clear whether the enhanced production of the hormone of the adrenal cortex in the anxious patient serves some useful purpose or simply represents a nonspecific action of the pituitary consequent to central nervous

system excitation brought about by the experience of anxiety.

Summary

Anxious subjects responded to intravenous corticotropin administration with an increase in hydrocortisone level in the plasma only slightly greater than that observed in normal subjects. At the same time anxious subjects excreted considerably larger quantities of hydroxycorticoids in the urine. As the dose of corticotropin was progressively raised over four days of testing, the urinary hydroxycorticoid increased to a greater degree in anxious subjects. After repetitive stimulation by infusion of corticotropin, the plasma level of hydrocortisone prior to each day's corticotropin administration rose progressively in the anxious subjects, whereas the level in the normal controls stayed constant. The results of these experiments, taken into consideration with previous findings, suggest that anxious subjects produce hydrocortisone at a rate several times as great as that of the normal subject. On the basis of indirect evidence, it is further hypothesized that the hypercorticoidism of the anxious subjects is a result of primary overactivity on the part of the anterior pituitary gland.

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Temporal Heart-Rate Patterns in Anxious Patients

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This report demonstrates an approach to the problem of describing pattern in repeated measurements and presents the result of an investigation of heart-rate patterns in a group of anxious patients. We attempted to answer two questions: Are there subgroupings among subjects in heart-rate patterns, and, if there are, do these groupings of subjects differ in other variables studied? These problems were approached within the context of a larger study of concomitant variation of affective, psychological, and physiological functioning under the impact of experimentally produced anxiety, conducted at the Institute for Psychosomatic and Psychiatric Research and Training of Michael Reese Hospital over the past three years. A complete description of the theory and methodology underlying the large study may be found elsewhere.[1]

Subjects and Procedure

The subjects were 19 adults, 13 men and 6 women, ranging in age from 22 to 57 years, with a mean age of 39, all but one of whom were inpatients at the Institute. They were clinically

selected as anxious or anxiety-prone. An attempt was made to exclude manifestly psychotic subjects.

Subjects were told very little about the nature of the experiment, only that they were taking a series of "tests." The experimental situation itself was imposing and potentially frightening. Subjects were hooked up to a maze of wires, and there were all sorts of impressive machinery prominently visible in the experimental room.

Each subject served on four successive days in the same laboratory. Preliminary measures were obtained on the first day, in the absence of any imposed stress. On each of the three experimental days there were a series of tests and measures preceding an anxiety-inducing psychiatric interview (the stress), and these same tests and measures were again repeated after the stress. These tests, in the order administered, were, first, a visual perceptual test (Area Judgment Test); second, the drawing of a blood sample (for biochemical assay), and, third, an evaluative (nonstressful) psychiatric interview. Measures of heart rate, respiration rate, and total body movement were recorded continuously throughout all sessions on an EKG pen writer located in another room. Subjects were observed continuously through a one-way-vision mirror by observers who accumulated notes on which to base ratings of anxiety, anger, and depression. Separate ratings covered the time preceding, the time during, and the time following the stress.

For present purposes the continuous heart-rate recording, covering a period of two hours or more, was subdivided and averaged within 15 subperiods. These subperiods were defined by the seven occasions when an experimenter was in the room with the subject (the two occasions of administration of each of the three tests plus the stress interview) and by the eight occasions when the subject was alone in the experimental room (preceding the first test, between each of the experimental procedures, and following the last test). The subperiods varied in length; those for the blood sample were short, while those for the interviews were relatively long. No weighting for length of subperiod was employed. These averages were then summed over the three days within each subperiod, yielding a series of 15 consecutive sums for each subject, each sum, in effect, representing

the subject's average heart rate during a particular phase in the experimental sequence.

Results

On inspection of the heart-rate means for the experimental periods, it became apparent that subjects differed considerably in the patterning of these 15 values. This observation led to two related questions: (1) Were there subgroupings of subjects having similar patterns, and (2) would these subgroupings differ in other respects as well? In order to get a quantitative measure of pattern similarity among subjects, these 15 average heart rates for each subject were taken as entries in product-moment correlations computed between subjects. Each of these correlation coefficients expresses the degree of similarity of the heart-rate patterns of the two subjects included in the correlation. If we interpret these subject heart-rate means as "tests" in the factor-analytic sense, the present analysis is, in effect, an exemplification of S technique, as proposed by Cattell.[2] The matrix of intercorrelations between all pairs of subjects appears in Table 1. The subject numbers 12, 13, and 14 were arbitrarily assigned to the three subjects who did not complete the experiment; hence the jump from 11 to 15 in this and in subsequent Tables.

Now, if all subjects were to have a similar pattern of heart rate from the beginning to the end of the experimental day, there would be a matrix resulting in which all the entries, that is all the correlation coefficients, would tend to be quite high and positive. The first centroid factor would then extract virtually all of the common variance in this matrix. The matrix was factored, and no such general factor emerged.

Instead, two significant centroid factors were obtained from this analysis. The communalities were judged sufficiently stable after one refactoring of the matrix. These factors seem to yield a simple structure solution[3] on rotation, most of the subjects having a high positive loading on one axis and a zero or small loading on the other. An

Table 1.—Matrix of Intercorrelations Between All Pairs of Anxious Patients

TABLE 2.—*Centroid Factor Matrix Prior to Rotation, with Communalities*

Subject	I	II	h²
1	0.23	0.51	0.31
2	0.04	0.54	0.29
3	0.62	-0.66	0.82
4	0.33	0.50	0.36
5	0.88	0.07	0.78
6	0.65	0.41	0.59
7	0.93	-0.24	0.92
8	0.05	0.75	0.57
9	0.84	-0.25	0.77
10	0.78	-0.52	0.88
11	0.15	0.24	0.08
15	0.25	0.59	0.41
16	0.61	-0.47	0.59
17	0.37	0.47	0.36
18	0.17	-0.38	0.17
19	0.86	-0.40	0.90
20	0.36	-0.40	0.29
21	-0.08	0.17	0.04
22	0.67	-0.59	0.80

oblique solution was utilized, with correlation of .15 between the two factors. Table 2 presents these centroid factors prior to rotation, with communalities. The matrix of transformation is in Table 3, and Table 4 contains the final rotated factor loadings. A plot of the original centroid factors, the planes A and B of rotation, and the subject groupings A and B appear in Figure 1.

Two subgroups of six subjects each were isolated for further study; each subgroup consisted of subjects who had very low or vanishing loadings on one of the axes and high loadings on the other. These subgroups, which we shall now call Groups A and B, are represented by the points within the circles. Thus, each group consists of subjects whose heart-rate patterns are similar to each other but are dissimilar to those of subjects in the other group. Figure 2 presents the mean heart rate on each of the 15 occasions for each of the two groups (N=6) and, for comparison, the average pattern for all 19 subjects. Despite the apparent differences in pattern, the over-all means (all occasions combined) and variances of the two groups do not differ significantly.

TABLE 3.—*Transformation Matrix* (λ)

	A	B
I	0.912	0.545
II	-0.410	0.838

Most subjects' between-days variability was far less than the between-subjects variability analyzed here. Typically a subject's patterning as analyzed by individual day tended to remain highly correlated with the group in which he belonged. In some cases, however, one of the three days might differ from the subject's patterning on the other two days, and consequently from the pattern of the group with which he was highly correlated. Group A is characterized by a very high initial level, followed by a gradual decline throughout the rest of the experimental session, with negligible elevations during the various experimental procedures. The patterns of subjects in this group were highly intercorrelated, and the loadings on this factor were very high. By contrast, the members of Group B have somewhat lower loadings on their factor, and consequently there is greater individual variation from their average curve. Unlike

TABLE 4.—*Final Rotated Factor Matrix*

Subjects	A	B
1	0.00	0.55
2	-0.18	0.47
3	0.84	-0.22
4	0.10	0.60
5	0.77	0.54
6	0.42	0.70
7	0.95	0.31
8	-0.26	0.66
9	0.87	0.25
10	0.92	-0.01
11	0.04	0.28
15	-0.01	0.63
16	0.75	-0.06
17	0.14	0.60
18	0.31	-0.23
19	0.95	0.13
20	0.49	-0.14
21	-0.14	0.10
22	0.85	-0.13

Group A, these subjects start the experimental session with a relatively low level of heart rate. Thereafter, the over-all trend is a very slight increasing one, with a marked increase in rate during the stress interview and during both periods of blood drawing. Note that while the curve for all subjects combined shows to some degree the salient characteristics of each of the subgroups, it does, of course, reduce the distinctiveness of either pattern.

The two groups isolated on the basis of heart-rate patterns were compared in terms
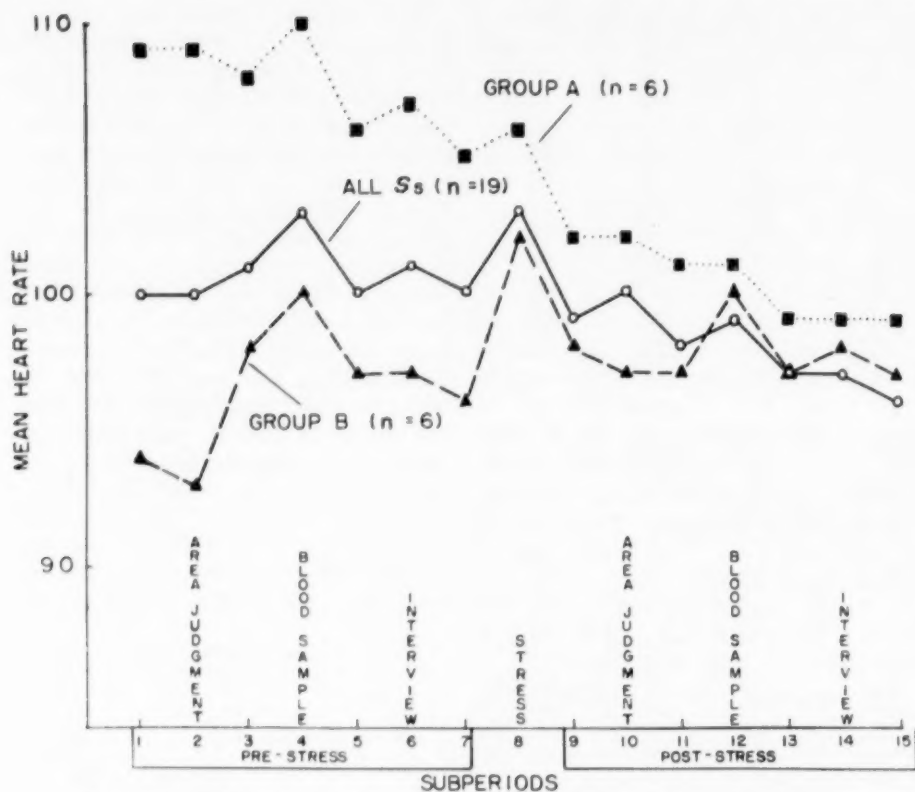
Fig. 1.—Comparison of mean heart rates for factorially derived subgroups with mean for all subjects.

of the variables in the experiment to discover whether they were distinguishable in other respects. The most clear-cut relations are to be found with the emotional variables. When the ratings of anxiety, anger, and depression made by the psychiatric observers are averaged over the whole experiment for each subject, we find that the mean anxiety rating for Group A is significantly higher than that for Group B at the .05 level ($t = 2.70$). Similarily, the mean rating for depression is higher for Group A than for Group B at the .01 level ($t = 3.93$). The groups did not differ in ratings of anger. In each of these comparisons the means for the remaining seven subjects were between those of the A and those of the B group, and were not significantly different from either.

Additional clinical evaluations had been made of each subject based on case-history material and on interview before the experiment. Because of the multiplicity of categories and the small number of cases in each of our groups, these data are less readily tested. However, Group A was generally characterized as lower in ego strength (in terms of two interdependent aspects—reality testing and anxiety control) and higher in anxiety proneness; by contrast, Group B tended to be relatively high in ego strength and lower in anxiety proneness. Thus, subjects who are more emotionally disturbed, both generally and under the specific impact of the experimental stress, tend to show less specific response in heart rate to the focal stresses of the experiment. It would seem that they

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PLANE B

GROUP A

GROUP B

PLANE A
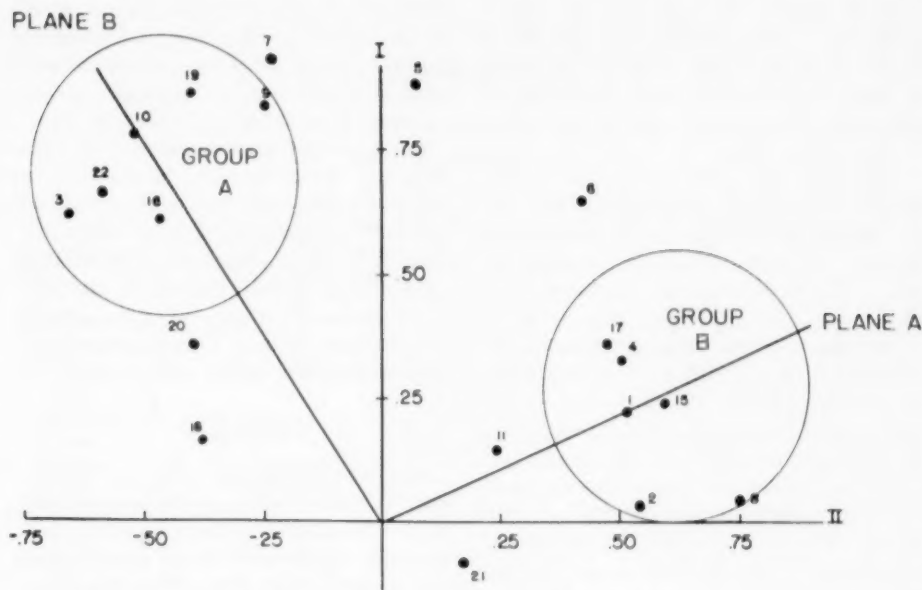
Fig. 2.—Factor plot of product-moment correlation of subperiod heart rate means between subjects.

respond maximally to the early part of the experimental day, and for the remainder show a pattern of gradual adaptation. On the other hand, those who have a somewhat lower level of emotional disturbance show heightened reaction to the expected focal threats.

Comment

Several conclusions are suggested by the data we have just presented. First, in studying processes such as the heart-rate response to various stimuli, it is probably not sufficient just to specify the experimental stimuli, in our case the various test procedures and the "alone" periods between them, without considering systematic individual differences in response to those stimuli. In the present case different levels of anxiety and depression ratings were associated with the two patterns of heart-rate response isolated. Further analyses suggest that the kind of anxiety experienced and, grossly, the initial clinical status of the patient are associated with differences in the patterns of heart

rate. Thus, simply averaging across all subjects shows no apparent experimental effect; yet we have seen that this conceals two very distinct patterns of response.

The two patterns which have emerged would seem to reflect two theoretically important modes of experiencing a stress situation, either in general or at least of the experimental sort studied here. The interpretation of the B pattern is straightforward. These subjects have a relatively level heart rate over the entire day, with distinct rises in immediate response to the most threatening procedures—the stress interviews and blood drawings—which thereafter returns to the original levels. Generally, they are among the less anxious of the subjects studied, both in terms of the chronic emotional disturbance with which they enter the experiment and in terms of the affective response to the experimental conditions. By contrast, the A pattern is found among the least well-integrated and more disturbed subjects. In heart rate, they are characterized by a higher level generally and show no indica-

tion of specific increment to the stress interviews or blood drawing. Rather, there is an over-all lowering of heart rate from the beginning to the end of the experimental day, with no discernible peaks related to any of the specific events.

The more disturbed subject, we might suppose, starts each experimental day with a distinctly greater amount of anticipatory anxiety. Taken from familiar surroundings and people, with whom he has worked out some mode of adjustment, he is more acutely aware of the potential threats in the strange laboratory, with its imposing wires and machinery and the business-like, but somewhat cold, experimenters. Despite repeated trips, the initial threat of the unknown is retained from day to day, although, once in the situation, there is gradual adaptation. However, against this heightened disturbance to the situation in general, the more specifically stressful events (as viewed by the experimenters) have no particular prominence. The highly anxious person in this as in many life situations is characterized by generally diffuse cognitive structure; to be in the experiment in the first place is the stress; the various events are not differentiated as possibly involving differing degrees of threat. With somewhat less anxiety, a patient becomes less sensitive to the implicit threats of the situation in general and, simultaneously, is more capable of distinguishing and reacting to the more explicitly disturbing events. In the sense that he parallels the experimenters' definition of stress in the situation, he might be described as more "realistic."

The A group's decrease in heart rate during the two-hour period warrants a methodological aside. Many experiments comparing the response to two successive conditions or contrasting "pre" and "post" measures to evaluate the effect of some intervening condition make the implicit assumption of a stable level of functioning, with no change due to time in the experiment as such. However, in view of the trends found in these data, one wonders whether in many studies of the effect of

emotional processes on heart rate it would not be better to determine an empirical base line against which to evaluate observed changes, rather than automatically assuming stability of functioning through time.

Most generally, however, we feel that this study has shown that the analysis of repeated measures may give information not contained in estimates of level and variability. As variance contributes information not contained in the mean, so, in the same way, a statement of pattern, by considering the relation with time, contributes information not contained in the variance.

Summary

In a multidisciplinary study of anxiety, heart rate was measured continuously during a series of discrete periods on three successive experimental days. These periods were defined by a series of test procedures administered before and after a psychiatric stress interview. Heart rate was averaged over the three days for each of the periods. Intercorrelating subjects yielded two relatively independent clusters of temporal heart-rate patterns. These groups of subjects also differ significantly in personality and affective response and seem to represent distinct modes of cardiovascular response in a psychological stress situation. The study further demonstrates that multivariate techniques, such as that described here, can be applied profitably to the analysis of pattern in physiological data and that such analysis can be fruitful in establishing psychophysiological relationships in the study of anxiety.

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News and Comment

The American Board of Psychiatry and Neurology, Inc.—After examination in New Orleans on March 18 and 19, the following candidates were certified in Psychiatry by the American Board of Psychiatry and Neurology, Inc.

Angres, Erwin, Chicago
Archer, Dean Robbins, Agnew, Calif.
Armistead, Charles Wrightsman, Houston, Texas
Atkinson, Rosser Payson, Boston
Berman, Leo H., Norwalk, Conn.
Boszormenyi-Nagy, Ivan, Syracuse, N. Y.
Brennan, Walter J., Alexandria, Va.
Brissenden, Arik, Cincinnati
Brown, Gordon Taylor, Indianapolis
Budd, Richard D., Northville, Mich.
Burch, Neil Robinson, Houston, Texas
Callan, John R., San Antonio, Texas
Carlson, Eric T., New York
Chambers, William Norman, Jacksonville, Fla.
Cochran, William L., Topeka, Kan.
Cornelison, Floyd S., Jr., Wellesley Hills, Mass.
Currier, Laurence M., Fort Sam Houston, Texas
Dean, Henry Leon, Norristown, Pa.
del Toro-Duncan, Luis, Santurce, P. R.
Dredge, Thomas E., St. Cloud, Minn.
Easterling, Walter Sidney, Baltimore
Elliott, Robert N., Detroit
* Epstein, Arthur William, Charleston, S. C.
Estes, Hubert R., Bellaire, Texas
Feigley, Charles Anderson, New Orleans
Finn, Murray E., Fort Knox, Ky.
Freeman, Victor J., Pittsburgh
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Books

The Criminal, the Judge, and the Public: A Psychological Analysis. Franz Alexander,
M.D., and Hugo Staub. Revised edition with new chapters by Franz Alexander, M.D.;
original edition translated by Gregory Zilboorg, M.D. Price, $4.00. Pp. xxii+239. The
Free Press, 1005 Belmont Ave., Chicago, Falcon's Wing Press, Indian Hills, Colo., 1956.

This is the second revised edition of a pioneering sociopsychological study in criminology
that achieved wide acclaim in both popular and psychiatric circles. A quarter of a century
has passed since the publication of the first English edition. During this period Alexander
has written four articles pertaining to the general subject matter of the book, and these are
appended as chapters of the present edition.

There is a new preface, in which Alexander briefly reaffirms his position of advocating
that the criminal should be regarded as "sick," and he hails the Durham decision as a legal
event that has finally made the thesis of this book a social reality. The book is divided into
two parts. Part I is devoted to "The Problem of Crime in the Light of Psychoanalytic
Theory," and in it there are discussions, for example, of "criminality as a general human
manifestation" and the "neurotic criminal," "a psychoanalytical table of criminological diag-
nosis," and a chapter on psychic determinism and responsibility. Part II is entitled "Some
Criminal Cases in the Light of Psychoanalysis." It contains several case studies, as well as a
chapter on the social psychology of punishment and another on psychiatric contributions to
crime prevention. The book is well made, and it is very readable. There is, however, no
bibliography and no index.

In view of the subject matter and the time that has elapsed since the book's first publication,
any attempt to assess its merits or shortcomings must deal with at least four (or more)
fairly discrete aspects of this work. In other words, historical, philosophic, sociopsychological,
and psychoanalytic considerations are all relevant to a balanced appraisal of this work. One
cannot do justice, in a review, to the complex problems that are raised. This reviewer will,
therefore, limit himself to a few comments of a general nature and will then proceed to
discuss in greater detail some special features of this book that are of interest from an
historical and psychoanalytic point of view.

This book was the first attempt to apply psychoanalytic concepts to an explanation of
criminal behavior. As such, it was bound to be interesting and richly rewarding. Today, the
relevance of psychoanalytic insight into any form of human behavior is taken for granted
by the serious student of human psychology. For a psychoanalytic author, this is both an
advantage and a handicap. It is an advantage insofar as it is no longer necessary to convince
others that there is an unconscious, that aggression is important, or of similar generalities.
At the same time, the mere demonstration of an unconscious motivation is felt, by many, as
rather empty. How does it follow from the demonstration of so-called neurotic motives for
crime that the criminal should be "treated"? This looks like a logical inference but it is not.
Decisions concerning which persons should be favored, and which abused, in society belong
to ethics and politics, not psychoanalysis. The authors gloss over the ethical problems in
their explicit effort to replace "punishment" by (compulsory) "treatment."

Alexander and Staub stated the original aim of the book as follows: "We want to under-
stand the criminal in order to be able to judge him correctly, so that our judgement may
be just beyond question" (p. xix). This assertion implies a type of logical connection between
psychological understanding and social action which, in the opinion of this reviewer, does
not obtain.

From a sociological point of view, the essential thesis of the book is that the ("neurotic")
criminal is "sick" and should be treated by psychoanalysis. Punishing such criminals only
makes them more entrenched in their habitual mode of behavior. This social custom, according
to the authors, expresses the aggression which society and the legal profession (the judge)
"take out," so to speak, on the criminal. In this connection, it would seem that the authors

proceed in their examination of the judge's social role in an unwarranted manner. They claim that the judge should be able to "understand human behavior" (p. 66). This was true of the "judge" in Biblical times, when he was philosopher, psychotherapist, and social arbiter all rolled into one. But is this his role today? The judge's role is to know and to interpret the law—not human beings! After all, that is what he is taught in law school. And, indeed, judges often publicly state their personal regret over having to render a particular verdict. Insofar as the authors felt that the laws governing the disposition of criminals should be changed—and this is apparently what they had in mind—it would have been better to make this clear in terms of the legislative changes that they advocate. Whether such changes should, or should not, be made is a valid and important question—but one that cannot be decided on solely psychoanalytic grounds.

This book is interesting and rewarding, finally, for the light that it throws on some of Alexander's later ideas. Among these, perhaps the most interesting is his reference to Victor Hugo's "Les Miserables." He wrote:

"In cases of such criminals the most effective mode of treatment would prove the one which Victor Hugo imagined in *Les Miserables*, in the case of the priest who was attacked by a robber. The priest, instead of imposing punishment, which the criminal unconsciously hoped to obtain, responded to the crime with kind deeds. This mode of action, we believe, would prove in the cases under consideration a much more effective preventive method than any form of punishment; for punishment results in little more than the fact that the criminal experiences a sense of relief; it gives him a sense of having expiated his sins and thus reduces his inhibitions; kindness, on the contrary, would increase still further the inhibitory power of his Superego, which is fundamentally so excessively strong in a neurotic criminal" (p. 57).

In this excerpt there is an early precursor of Alexander's later formulations concerning "role-taking" and the "corrective emotional experience." Without wishing to add to the controversy on this subject, this reviewer wants only to call attention to the following considerations: 1. From an historical perspective, it is interesting that the notion of the "corrective emotional experience" apparently originated from the study of "criminals," and was later applied to "neurotics." The goal of making the criminal socially conforming may provide an important clue to our understanding of this theoretical construction. 2. In the introduction, Alexander and Staub stated explicitly that insofar as there is a conflict between the criminal and society, they side with the interests of the latter (p. xviii). In the example cited, they side with the superego against the ego. They do this in spite of their own assertion that the inhibitory power of the superego is, in such persons, excessively strong. Should not a psychotherapist, however, ask himself whether he is really helping his patient by putting him into a psychological strait jacket even tighter than that in which he was before? 3. Lastly, assuming that the authors are correct in identifying the significant mechanism in at least some criminals as one pertaining to guilt and self-created attempts to expiate, it would follow—or so it seems to this reviewer—that such a maneuver should rightly be viewed as a sort of self-therapy on the part of the criminal. When this mechanism has run its course, maybe sometimes after several repetitions of crime and punishment, perhaps the ego will have "healed" to some extent. The authors do not permit this possibility. Yet, by excluding the very possibility of this self-healing mechanism, and by advocating that the criminal be literally tricked by "kindly" behavior when he expects "punishment," is not one really subjecting him to a subtler form of mental coercion? And, if so, is this desirable? The authors persistently equate therapeutic intent with (unquestionably) beneficent results and thereby short-cut the occurrence of the problems mentioned.

Alexander's present views on the relationship of psychiatry and law are briefly stated in the new preface. They are, apparently, substantially the same as those set forth in the original text. Alexander advocates the large-scale participation of the "psychiatric expert" in criminal trials. Why? Because, we are told, "This would amount to an official recognition of unconscious motivation in all human behavior" (p. xiii). Why we need this sign of "official recognition" is not explained. "The neurotic criminal," Alexander continues, "obviously has a limited sense of responsibility. Primarily he is a sick person, and his delinquency is the outcome of his emotional disturbances. This fact, however, should not exempt him from the consequences of his action. If he is curable, he should be incarcerated for the duration of psychiatric treatment so long as he still represents a menace to society. If he is incurable, he belongs in a hospital for incurables for life" (p. xiii). Observational data, e. g., antisocial behavior, are here confused with the observer's frame of reference or ethical judgment, e. g., criminality or

sickness. The gallant advocacy of life-imprisonment (a hospital can be a jail, too) for the "incurable criminal"—presumably irrespective of his offenses—hardly requires comment.

In summary, this book is important and deserves careful study by all those interested in the relationship of psychiatry and law primarily because it is a pioneering contribution to what was, at the time of its original writing, an unexplored area of scientific inquiry. It is important, also, because of the scientific eminence of its principal author. It can be more highly recommended, however, to the serious investigator in this no man's land between psychiatry, sociology, ethics, and jurisprudence, than it can to the psychiatric novice or the laity. For, in reading this book, it is important to differentiate psychoanalytic observations, hypotheses, social inferences based on them, and ethical preferences—a differentiation which the authors rarely, if ever, make for the reader. The reader, therefore, will have to be able to do this for himself.

THOMAS S. SZASZ, M.D.

The Sentence Completion Method: Its Diagnostic and Clinical Application to Mental Disorders. By Amanda R. Rohde. Price, $7.50. Pp. 301. The Ronald Press Company, 15 E. 26th St., New York 10, 1957.

This book presents a thorough and detailed exposition of the Sentence Completion Test as a valuable clinical instrument. Dr. Rohde reviews the history of the technique and the existing variations before presenting instructions for administration, scoring, and interpretation. The scoring method used is essentially that of Dr. Henry Murray's need-press system devised for use with the TAT. This method allows for finer qualitative, as well as quantitative, analysis and comparisons and suggests the rich potential of this approach for training and for research use. One of the chief advantages which this technique has offered to practicing clinicians is that it allows for a relatively quick appraisal of personality aspects which supplement the findings of other, more basic techniques, and yields data that can be interpreted from a variety of conceptual frameworks. There is some question as to whether the elaborate and somewhat tedious scoring system offered here would add enough important clinical data to compensate for the additional time. The second section of the book explores the use of the technique for comparative studies and diagnostic differentiations among personality disorders of adolescents and adults, psychoneurotic and psychotic subjects. Twenty-three cases are presented in detail, and the more general findings from the larger group are discussed. Many of the findings which emerged are both provocative and suggestive of the usefulness of the method as a research tool.

The Social Problem of Mental Deficiency. By Neil O'Connor and Jack Tizard. Price, $5.00. (30s). Pp. 183. Pergamon Press, Ltd., 4-5 Fitzroy Sq., London, W. 1, 1956.

This small volume marshals a good deal of diverse evidence in its scientific call to a humanist approach to the mentally defective. The authors remind us quite forcefully that mentally deficient people are people first and mentally deficient second. When employment is high, most of these persons find work and make a reasonably good social and personal adjustment. Most of them are not seriously neurotic, delinquent, or psychotic. Most of them belong in the community, not in the hospital. Many an imbecilic child is not an imbecilic adult. Group and individual psychotherapy can make important differences in the lives of these human beings. Furthermore, we are urged to go beyond I. Q. tests in evaluating the cognitive functioning of the feebleminded and the imbecile.

The first portion of the book contains a historical background, an examination of the prevalence of mental deficiency, and the available mental deficiency services in Britain today. Using the available literature, the authors next attack excessive reliance on the I. Q. and on the equation of mental deficiency and personality disturbance. The next chapter is a report of two investigations of the prediction of work success by a battery of tests: intelligence, personality, dexterity, and so forth. As is all too customary these days, they report that past behavior is the best index for prediction. They become tied up in an argument with themselves about whether emotional instability is the most serious cause of occupational disability, and this reviewer is still confused about what they conclude. After this, they discuss an experimental workshop that they instituted. After eight months of troubled beginnings, the workship seemed to go smoothly. They think it helped the boys on their return to the community. Then follows the presentation of experiments with various types of supervision, with teaching defectives to read (in which substantial gains were made), with the use of incentives with imbeciles, and

with workshop activities of imbeciles. In all, the authors' humanist aims tend to be supported. They studied the occupational adaptation of these boys in the community and their response to psychologically oriented treatment. A discussion of administrative and legal changes needed

Much ground is covered, some in lucid fashion, some in more discursive fashion. Important precedes the conclusion.

issues are faced, and the authors are willing to use many kinds of evidence to resolve the issues; One finds scientific sophistication, clinical ingenuity, scholarliness, and a bit of prosely-tizing in this almost authoritative book. It deserves a wide audience.

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